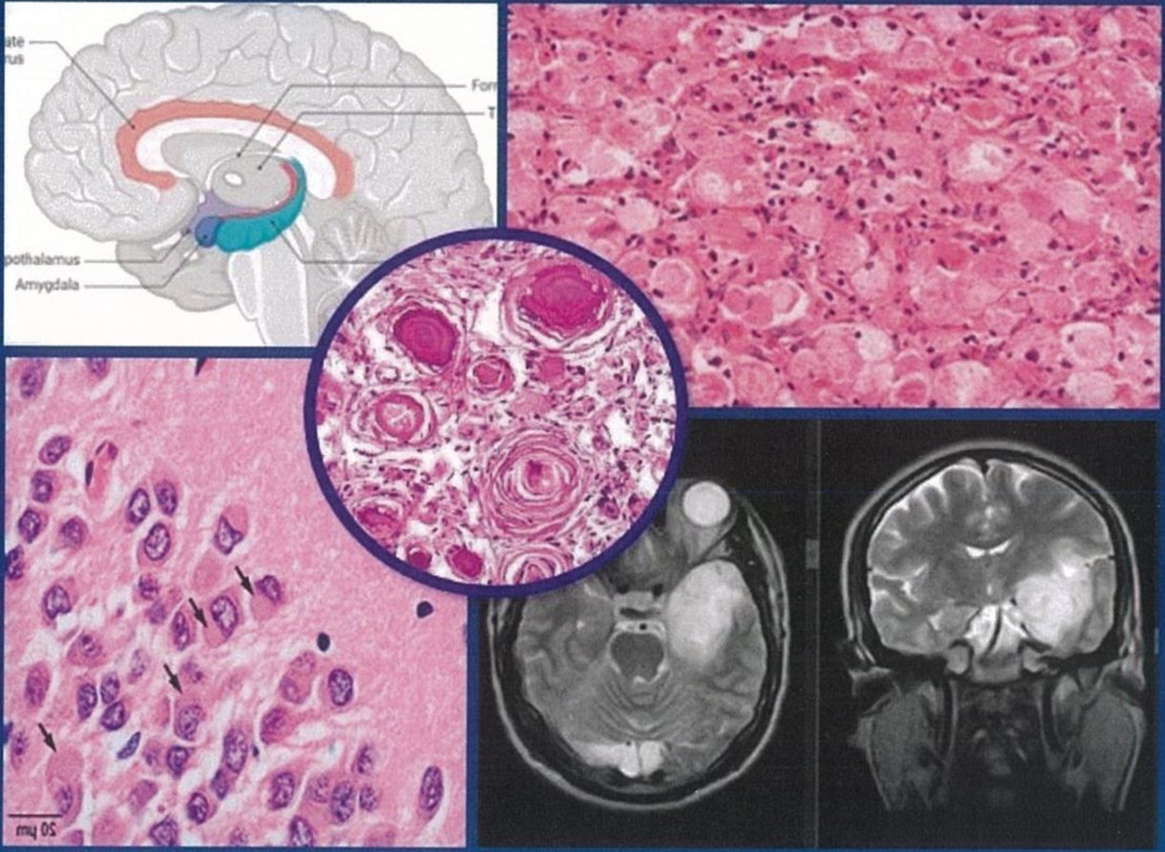
ACE THE BOARDS:

NEUROPATHOLOGY



pothalamus
Amygdala
20 µm

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ACE MY PATH
PathPresenter

First Edition

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FOREWORD

"I read Greenfield's… twice…" was a common refrain I heard when asking recent neuropathology graduates how they prepared for the board exam and what resources akin to First Aid for the USMLE were available to help direct my studies and bring the daunting and diverse field of neuropathology into manageable focus.

This innovative book represents a significant step forward in neuropathology education. It offers a unique approach tailored specifically for those preparing for the neuropathology board exam and serves as a quick reference guide for practicing neuropathologists. Designed by experts in the field, this book covers a wide range of topics essential for board exam preparation, from the fundamentals of neuropathology to newer advances in molecular genetics and emerging trends. Each chapter is meticulously crafted to provide clear and concise descriptions, high-quality images, and clinical correlations, ensuring a comprehensive understanding of the material.

By incorporating QR codes to access whole slide images, this book provides readers with an interactive experience that bridges the gap between the textbook and clinical practice. Gone are the days of static illustrations; now, readers can explore real-life neuropathological specimens with just a scan of their device. Whether you are a seasoned neuropathologist seeking to enhance your knowledge or a trainee embarking on your journey in the field, this book will be an invaluable resource. Its innovative approach not only facilitates exam preparation but also fosters a deeper appreciation for the intricacies of neuropathology.

I commend the authors for their dedication to advancing neuropathology education and providing a much-needed resource. I wish readers well as they take this important step in their professional development and hope it serves you well on your path to success in the challenging, rewarding world of neuropathology.

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PREFACE

Dear Readers,

In this inaugural edition of Ace the Boards: Neuropathology, our objective is to furnish residents and fellows with a concise yet comprehensive neuropathology review. Neuropathology is inherently broad, encompassing various areas such as neoplastic surgical neuropathology, neurodegenerative diseases, ophthalmic pathology, and muscle and nerve pathology during a two-year fellowship. Each neuropathology training program has its unique strengths, prompting trainees to focus on specific topics.

Our inspiration for this venture stems from the realization that, to the best of our knowledge, there is currently no quick review book catering to the diverse needs of neuropathology trainees. Ace the Boards: Neuropathology aims to fill this gap and provide a resource tailored to the specific requirements of those pursuing neuropathology training.

While acknowledging the availability of comprehensive reference textbooks, we want to emphasize that our goal is not to replace them. Instead, we strive to offer an easily digestible and quick neuropathology guide intended for residents, fellows, and practicing pathologists.

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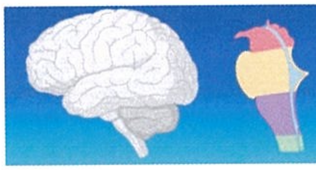

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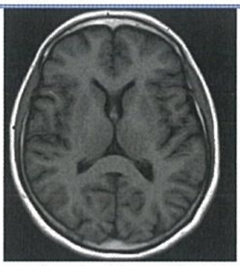
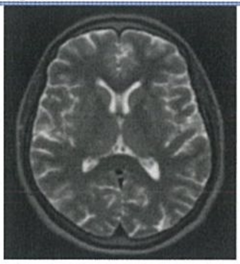
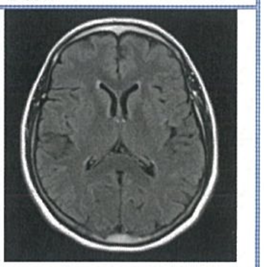
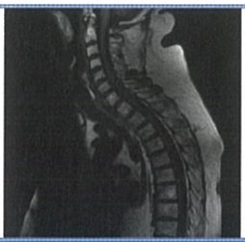
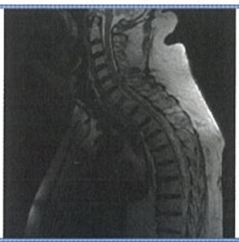
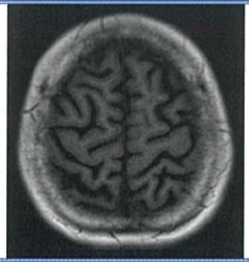
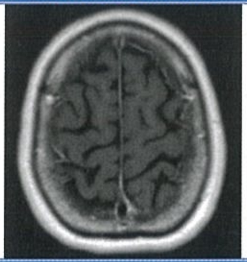
BASIC CNS PATHOLOGY

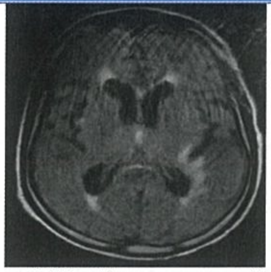
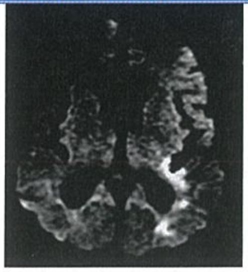
RAQUEL T. YOKODA, MD

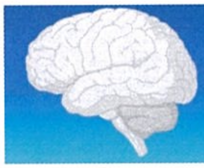
NEUROANATOMY – BRIEF RADIOLOGY PERSPECTIVE - MRI

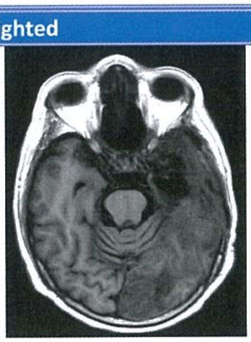
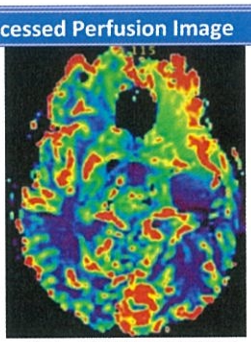
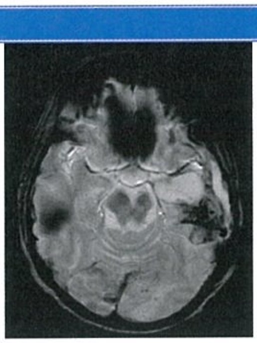
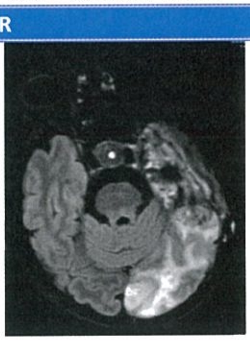
Tissue	T1-weighted	T2-weighted	FLAIR
Cortex	Gray	Light Gray	Light Gray
White Matter	Light	Dark Gray	Dark Gray
CSF	Dark	Bright	Dark
			

Tissue	T1-weighted	T2-weighted
Spinal Cord	Gray	Bright
Fat (Subcutaneous Tissue)	Bright	Light
Disc	Gray	Bright
Muscle	Gray	Dark Gray
Air	Very dark	Very dark
Inflammation Edema Infarction Demyelination	Dark	Dark
		

Observations	T1-weighted	T1-weighted with Gadolinium
• Gadolinium enhances bright signal in the vessels • Gadolinium can be detected in: ➢ Enhancing and non-enhancing gliomas ➢ Necrosis • Gadolinium can be retained in the adjacent normal brain (when evaluating gliomas)		

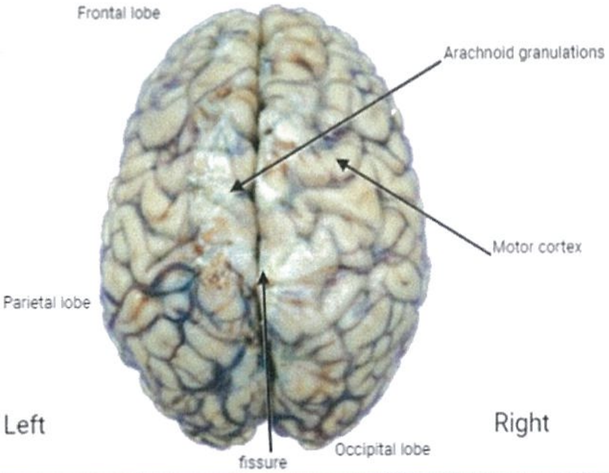
Observations	FLAIR	Diffusion-weighted (DWI)
• Acute infarction can only be seen in diffusion-weighted MRI • CT is better than MRI for acute hemorrhage • Figures: A curvilinear band of high FLAIR signal with associated diffusion is noted in the **posterior left** subinsular region, extending to the **left** periatrial parenchyma. Both may reflect recent infarction.	 FLAIR with movement artifact	



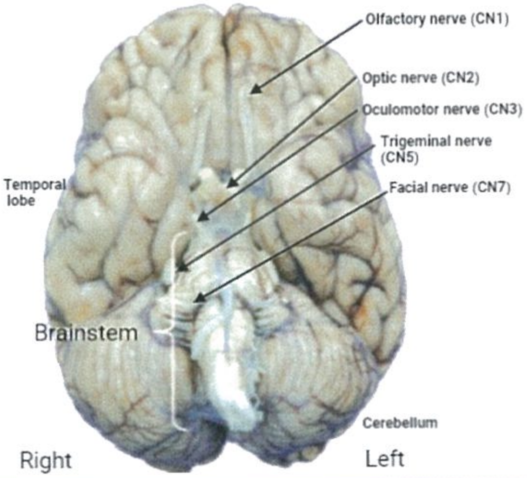
Perfusion MRI	T1-weighted	Processed Perfusion Image
- Image with overlay of color-coded cerebral volume map - A neoplasm can alter the surrounding blood flow; perfusion is helpful to assess disease progression/recurrence vs. treatment effect		 Red – high blood volume Blue – low blood volume
	GRE	**T2 FLAIR**
- GRE: Gradient echo - Helpful to identify blood products - Figures: The case has an area of hemorrhage close to a resection cavity. Blood products are highlighted in the GRE, and vasogenic edema highlighted in the T2-FLAIR		

NEUROANATOMY & NORMAL HISTOLOGY

SURFACE ANATOMY: DORSAL VIEW


Frontal lobe
Arachnoid granulations
Motor cortex
Parietal lobe
Left
Right
fissure
Occipital lobe

SURFACE ANATOMY: VENTRAL VIEW


Olfactory nerve (CN1)
Optic nerve (CN2)
Oculomotor nerve (CN3)
Trigeminal nerve (CN5)
Facial nerve (CN7)
Temporal lobe
Brainstem
Cerebellum
Right
Left

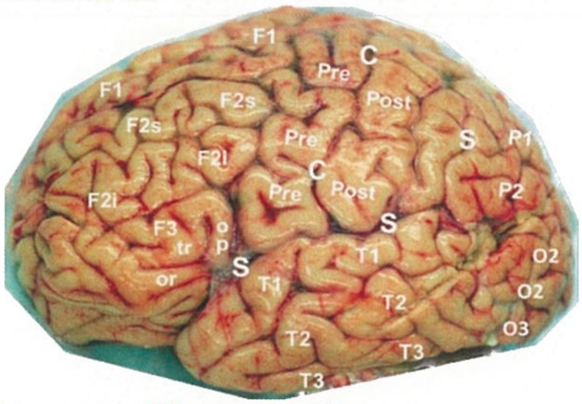
Superior = Dorsal
Inferior = Ventral
Anterior = Rostral
Posterior = Caudal
Trochlear (CNIV) is the only cranial nerve to exit the brainstem in the dorsal aspect

SURFACE FEATURES OF THE LEFT HEMISPHERE

- **Lateral convexity of the brain**
  - Frontal gyri: Superior (F1), middle (F2), inferior (F3)
  - Precentral gyrus (Pre)
  - Temporal gyri: Superior (T1), middle (T2), inferior (T3)
  - Parietal lobe: Postcentral gyrus (Post), superior P1, and inferior (P2)
  - Occipital lobe: Superior (not seen), middle (O2), inferior (O3)
  - Other anatomy landmarks: Sylvian fissure (S), central sulcus (C), pars opercularis (op), pars triangularis (tr), pars orbitalis (or)

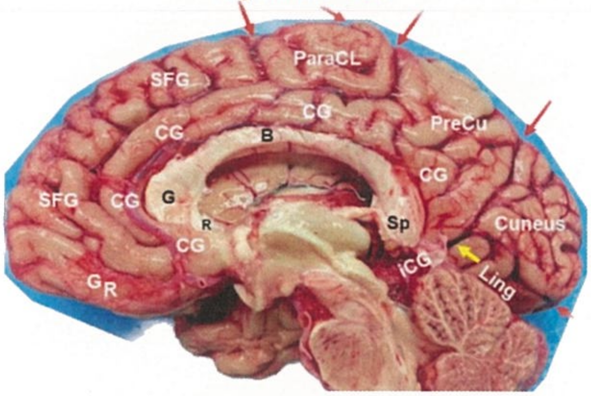
1. BASIC CNS PATHOLOGY

Lateral surface view


F1
F1
F2s
F2s
F2i
F2i
F3
tr
or
o
p
Pre
C
Post
Pre
C
Pre
Post
S
S
S
P1
P2
T1
T1
T2
T2
T3
T3
O2
O2
O3

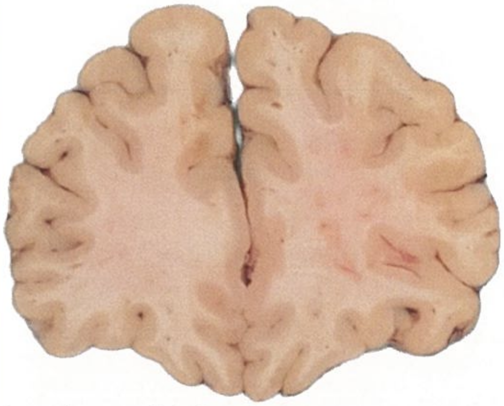
Pictures courtesy of Thomas Naidich, MD

Sagittal midline cut


ParaCL
SFG
CG
CG
B
PreCu
CG
G
SFG
CG
R
Sp
Cuneus
CG
iCG
Ling
GR

- **Medial surface of the brain**
  - Superior frontal gyrus (SFG)
  - Lingual gyrus (Ling)
  - Gyrus rectus (GR)
  - Cingulate gyrus (CG)
  - Isthmus of the cingulate gyrus (iCG)
  - Corpus callosum: Rostrum (R), genu (G), body (B), splenium (Sp)

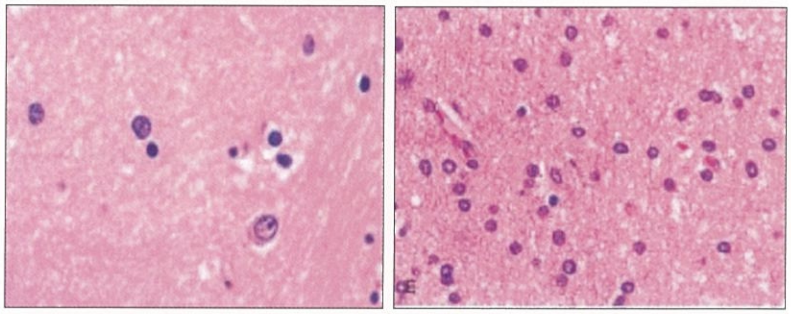
- **Sulci (indicated by red arrows, clockwise)**
  - Paracentral sulcus (ParaCS)
  - Central sulcus (CS)
  - Pars (M)
  - Parieto-occipital sulcus (POS)
  - Calcarine sulcus (Cal S)

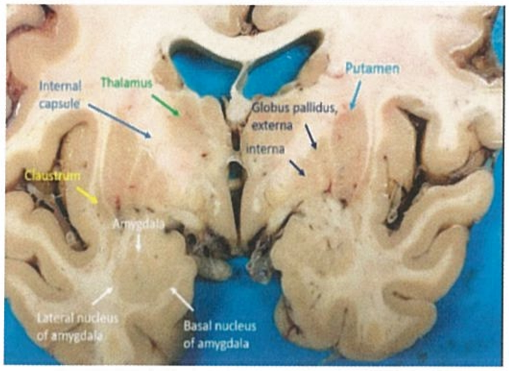


Coronal section of the frontal pole; gray matter is darker/outside; white matter is lighter/inside

FRONTAL POLE

- **Gray and white matter microscopy (below)**
  - Gray matter: Neuropil with large neuron
  - White matter: Oligodendroglia and axons

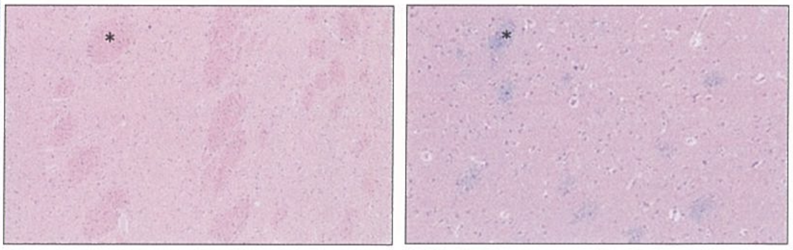


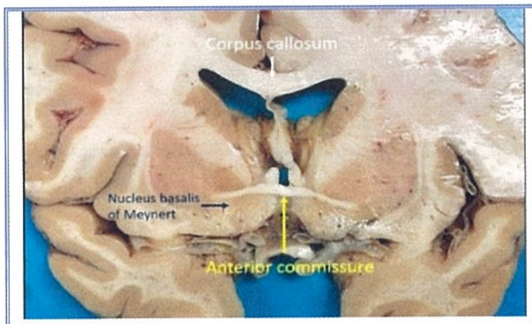

Internal capsule
Thalamus
Putamen
Globus pallidus,
externa
interna
Claustrum
Amygdala
Lateral nucleus of amygdala
Basal nucleus of amygdala

Coronal section at the level of the claustrum and insular cortex. Picture courtesy: Jamie Walker, MD, PhD

CORONAL SECTION

- **Basal ganglia, striatum, claustrum, amygdala, insular cortex**
- Microscopy below shows putamen with the pencil bundles of Wilson (asterisks), also known as pencil fibers of Wilson, in H&E (left) and LFB (right)

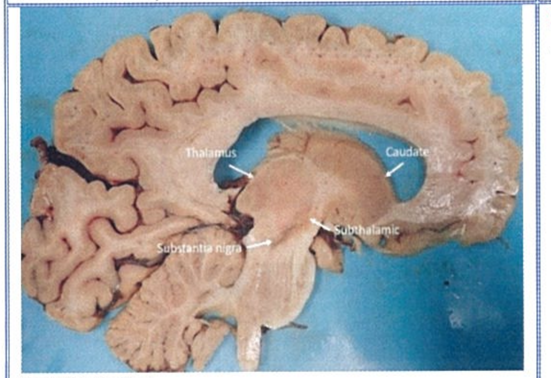



Corpus callosum
Nucleus basalis of Meynert
Anterior commissure

Coronal section
Picture courtesy: Jamie Walker, MD, PhD

CORONAL SECTIONS: FIXED BRAIN

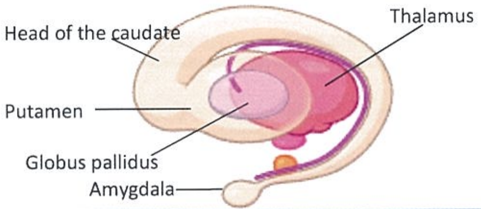
- **Base of the forebrain**
  - Interhemispheric white matter bundles: Corpus callosum and anterior commissure
  - Nucleus basalis of Meynert (substantia innominata) → provides the cortex with the highest supply of acetylcholine

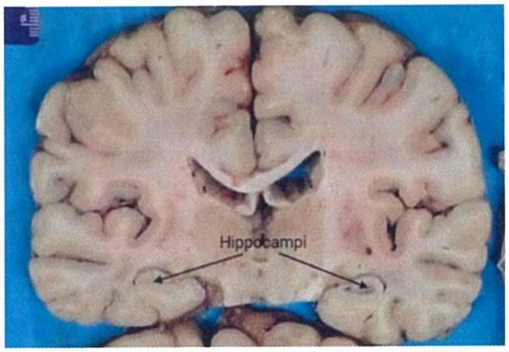

Thalamus
Caudate
Subthalamic
Substantia nigra

Sagittal section
Picture courtesy: Jamie Walker, MD, PhD

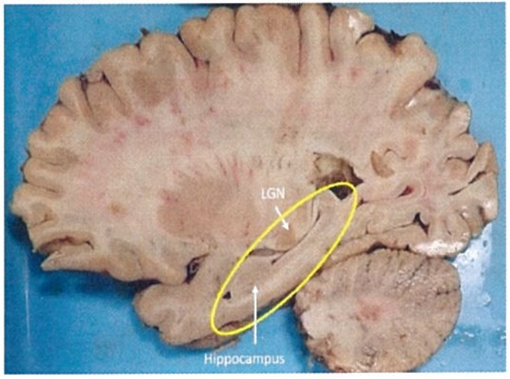
SAGITTAL SECTION: FIXED BRAIN

- **Caudate and thalamus**
  - Note the substantia nigra at the midbrain and anatomic relation with thalamus and pons
  - Note the position of the subthalamic nucleus
  - Note the position of the thalamus and the basal ganglia (caudate, putamen, globus pallidus) in the figure below (created with BioRender)


Head of the caudate
Thalamus
Putamen
Globus pallidus
Amygdala


Hippocampi

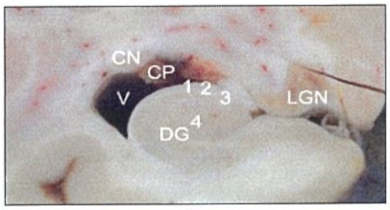
Coronal section at the level of hippocampi

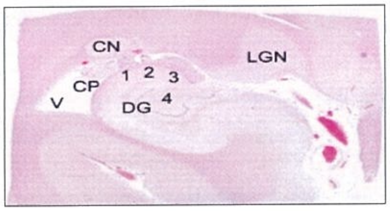

LGN
Hippocampus

Sagittal section
Pictures courtesy of Jamie Walker, MD, PhD

HIPPOCAMPUS FORMATION

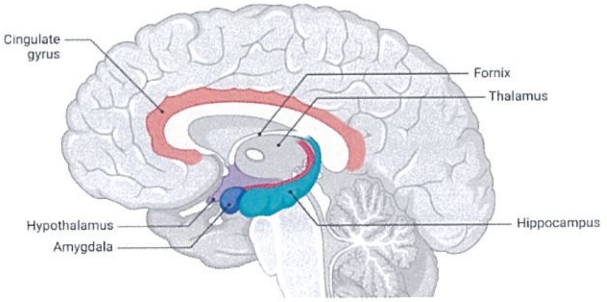
- Composed of the subiculum, cornu ammonis (CA)
- CA is subdivided into CA1-4 and the dentate gyrus (DG)
  - CA1 → Sommer's sector (most sensitive to ischemic-hypoxic insults, seizures, Alzheimer disease)
  - CA2 → dorsal resistant zone
- See below the lateral geniculate nucleus (LGN), tail of the caudate (CN), and dentate gyrus (DG)

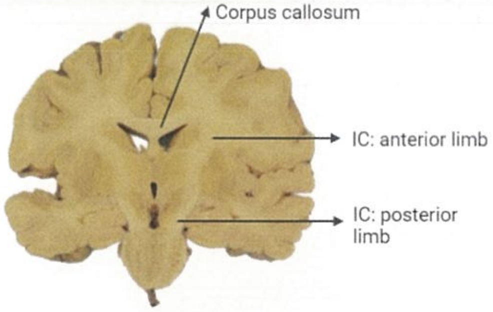

CN
CP
V
1
2
3
4
DG
LGN


CN
LGN
CP
1
2
3
V
DG
4

- The hippocampus is a long structure, better appreciated in sagittal sections (yellow circle on left and shaded in green below)

The limbic system, created with BioRender


Cingulate gyrus
Fornix
Thalamus
Hypothalamus
Amygdala
Hippocampus


Corpus callosum
IC: anterior limb
IC: posterior limb

Coronal section showing internal capsule

INTERNAL CAPSULE (IC)

- **IC is a subcortical white matter bundle**
- Allows communication between the cerebral cortex and areas of the brainstem
- Pathways inside the internal capsule are necessary for physical movement and sensory perception; descending and ascending tracts
- IC receives its vascular supply from perforating arteries that arise from the anterior cerebral artery, middle cerebral artery, anterior choroidal artery, and the internal carotid artery
- **Examples of fiber pathways in the IC**
    - ➢ Thalamocortical and corticothalamic fibers
    - ➢ Corticopontine, corticobulbar, corticospinal

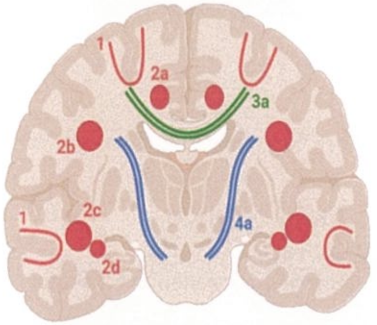

1
2a
3a
2b
2c
4a
1
2d

Image created with BioRender

WHITE MATTER TRACTS (CORONAL SECTION ON THE LEFT)

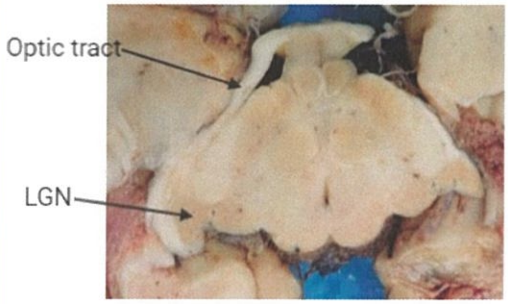
- Association fibers (connecting cortical areas within the same hemisphere)
- Commissural fibers (connecting cortical areas of the left and right hemispheres to one another; crossing the midline)
- Projection fibers (connecting cortical areas to subcortical, brainstem, and spinal cord structures)

1) Short association fibers

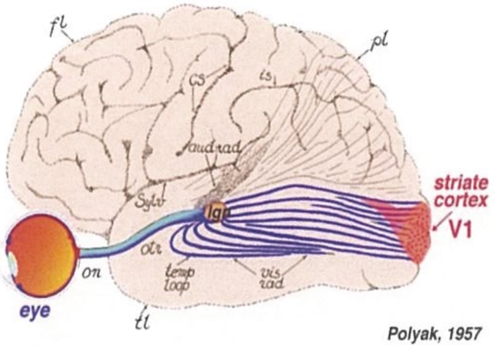
2) Long association fibers
- a) Cingulum
- b) Superior longitudinal fasciculus
- c) Inferior longitudinal fasciculus
- d) Uncinate fasciculus

3) Commissural fibers
- a) Corpus callosum

4) Projection fibers
- a) Internal capsule


Optic tract
LGN

Optic tract connecting to the LGN. Lamination at the LGN will define the pathway to the visual cortex (see drawing below)

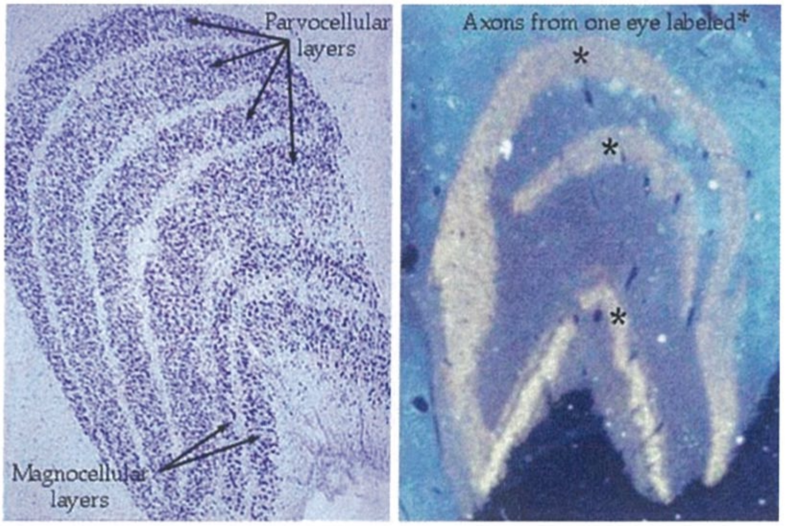

fl
pl
cs
is
audrad
Sylv
lgb
striate cortex
V1
otr
on
temp loop
vis rad
eye
tl

Polyak, 1957

Open-source Polyak drawing showing the optic tract to the LGN and visual cortex (V1)

LATERAL GENICULATE NUCLEUS LAMINATION

- LGN has specific lamination
- 6 layers, each with different pathway to the visual cortex
- Green → input retinal ganglion P cells – output visual cortex layer 4C beta
- Blue → input retinal ganglion M cells – output visual cortex layer 4C alpha
    - ➢ Mnemonic: "2 + 3 = 5 ipsi"
    - ➢ Marked (*) contralateral fibers (1,4,6) in the image below

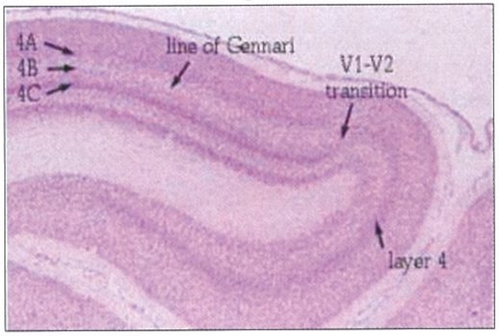

Parvocellular layers
Magnocellular layers
Axons from one eye labeled*
*
*
*

Each eye projects "alternating" layers as seen on the right. The projections reach the parvocellular and magnocellular layers of the LGN as seen on the left

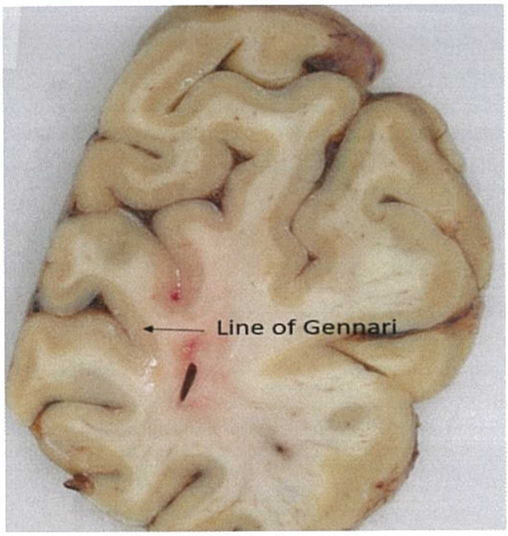
Picture courtesy: Dr. Matthew Schmolesky

CALCARINE CORTEX

- Marked by the line of Gennari
- Visual cortex (V1)
- Important in the evaluation of neurodegeneration


4A
4B
4C
line of Gennari
V1-V2 transition
layer 4

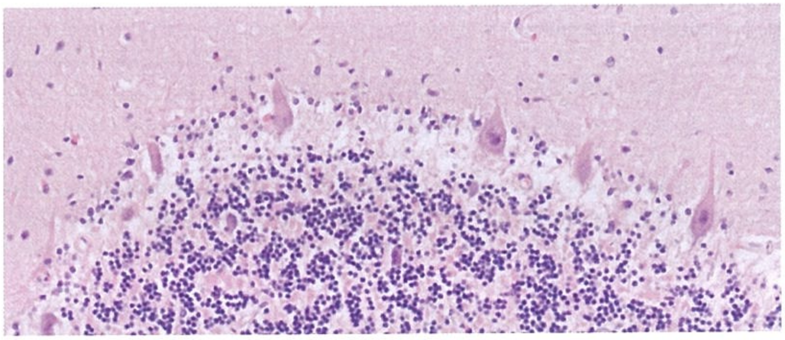
Microscopy showing the line of Gennari
Picture courtesy: Open-source image


Line of Gennari

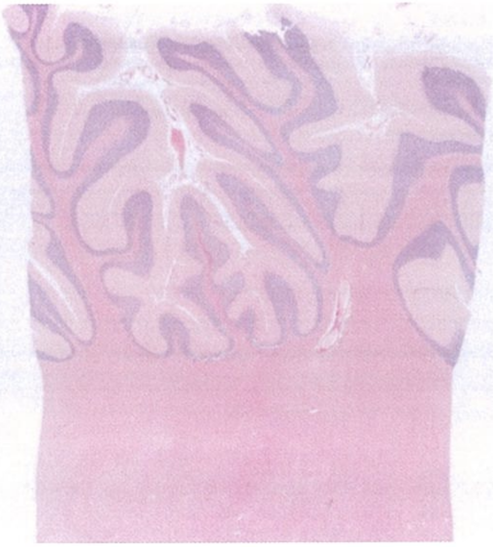
Gross picture of the calcarine cortex

CEREBELLUM

- Cerebellar folia
- Layers: Molecular layer/Purkinje layer/granular cell layer
- Purkinje cells – early dysfunction with ischemia
- Dentate nucleus – important in evaluating neurodegenerative diseases



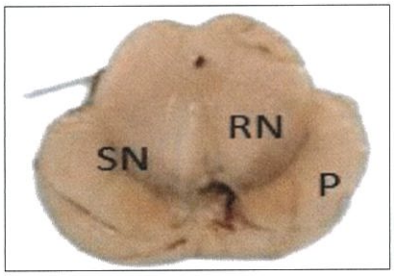
H&E (20x) showing the cerebellar layers, from top to bottom: Molecular layer, Purkinje layer, and granular cell layer

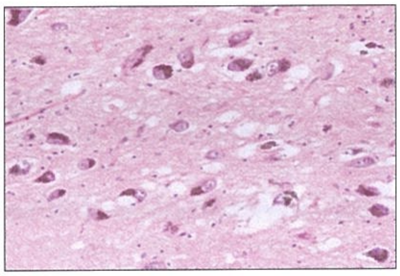


H&E showing low-power view of the cerebellar folia

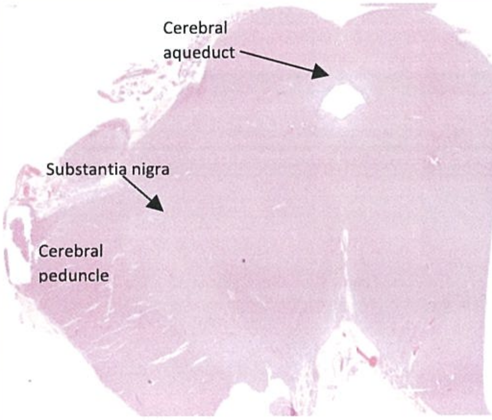
MIDBRAIN

- Aqueduct
- Red nucleus (RN)
- **Substantia nigra** (SN) – pars compacta and pars reticulata
- Peduncle (P)

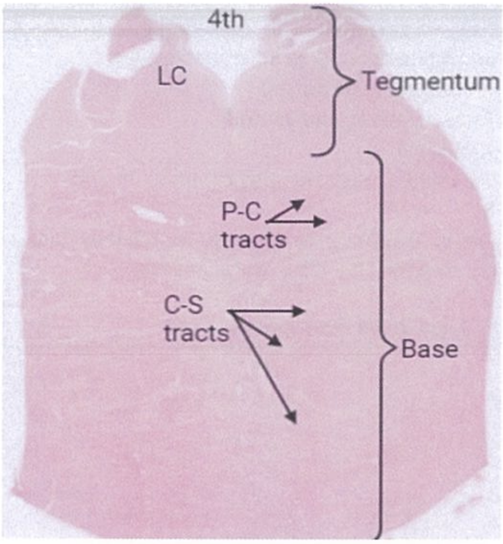




H&E showing substantia nigra, well pigmented


Cerebral aqueduct
Substantia nigra
Cerebral peduncle

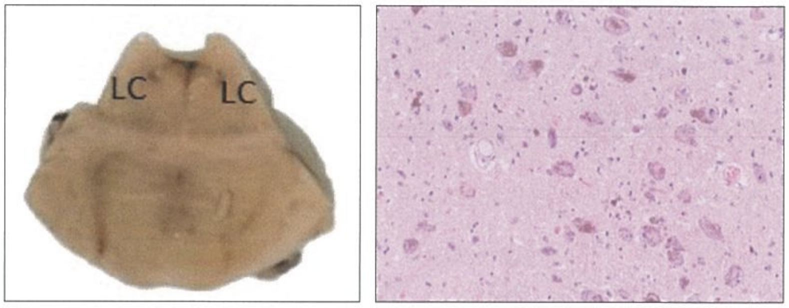
H&E shows midbrain at 1x


4th
LC
Tegmentum
P-C tracts
C-S tracts
Base

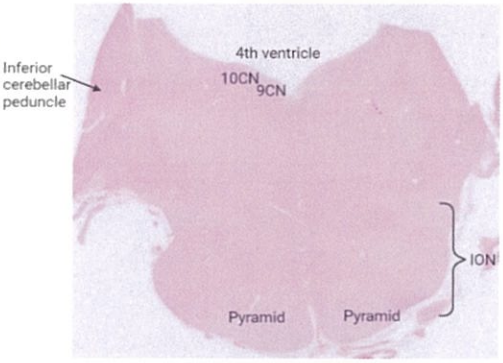
H&E showing low-power view of the pons

PONS

- Locus ceruleus (LC) (norepinephrine/catecholaminergic neurons) and tegmentum
- 4th ventricle
- Base: P-C and C-S
  - ➢ Pontocerebellar (P-C) tracts (darker in H&E)
  - ➢ Corticospinal (C-S) tracts (lighter in H&E)



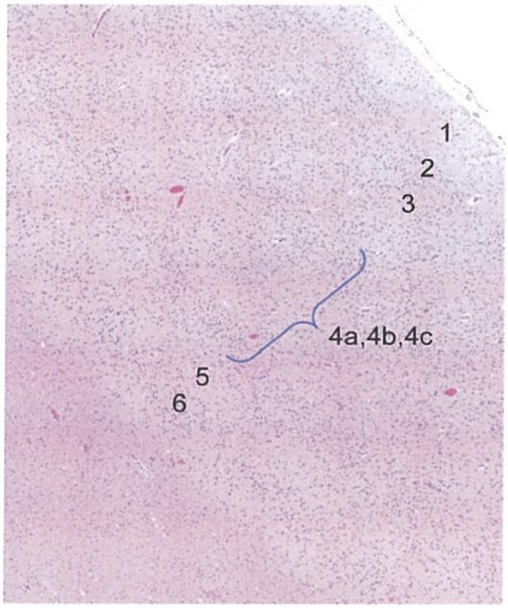
Locus ceruleus pigmentation on H&E


Inferior cerebellar peduncle
4th ventricle
10CN
9CN
ION
Pyramid
Pyramid

H&E showing low-power view of the medulla

MEDULLA

- 4^{th} ventricle
- Roof (tectum) and floor (tegmentum)
- Nuclei for 2 cranial nerves (CNX and CNXII)
- Inferior olivary nucleus (ION)
- Peduncle

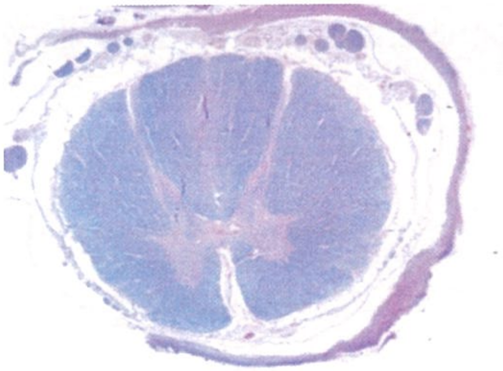

1
2
3
4a,4b,4c
5
6

H&E showing layers of the cerebral cortex

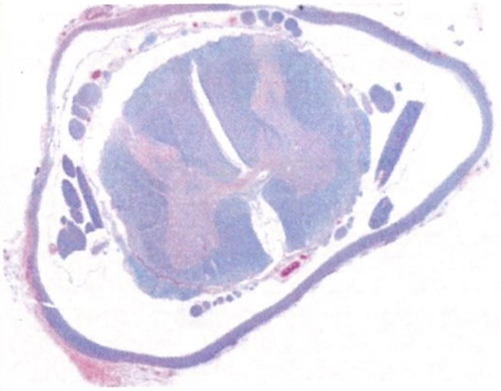
NORMAL CORTEX

- 6 layers (MGP-GPM)
  - ➢ Molecular (plexiform)
  - ➢ External granular
  - ➢ External pyramidal
  - ➢ Internal granular
  - ➢ Internal pyramidal
  - ➢ Multiform (fusiform) layers

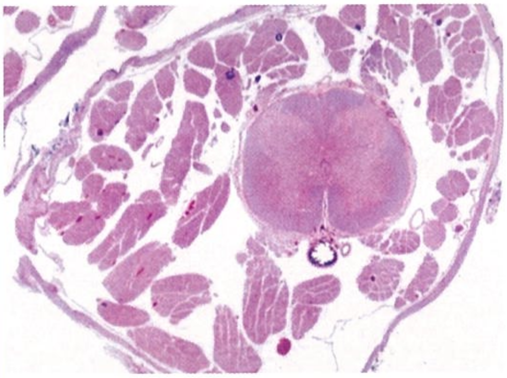
Path Presenter



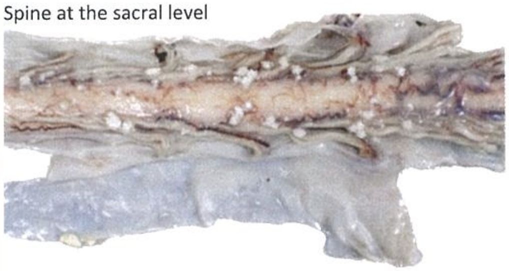
LFB stain showing spine at the thoracic level



LFB stain showing spine at the lumbar level



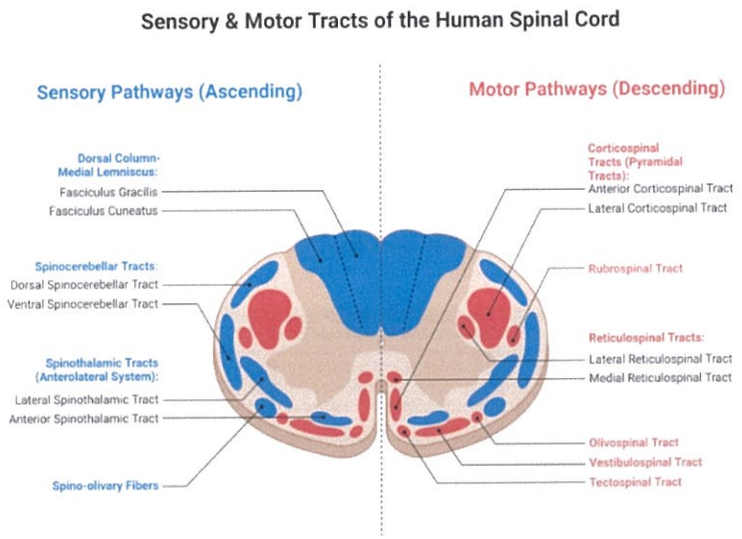
Spine at the sacral level



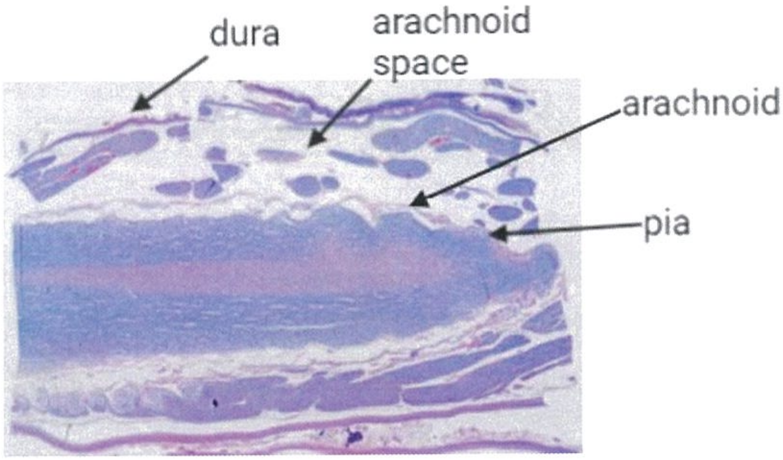
Arachnoid calcifications (usual finding, benign)

SPINAL CORD

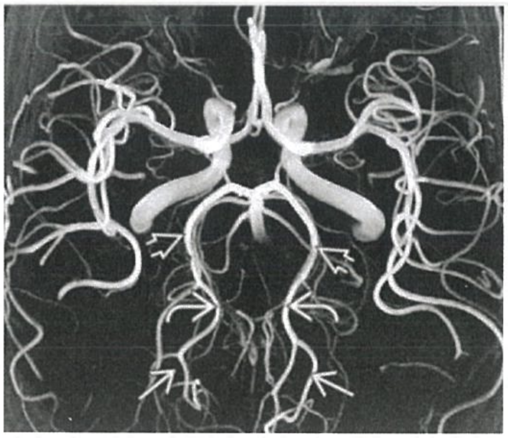
- Organization of the white matter and gray matter opposite to the brain (white inner/gray outer in the brain and white outer/gray inner in the spine)
- Gray matter forms horns (ventral, lateral, and dorsal)
- White matter forms columns (dorsal, lateral, and ventral)
- In the middle, there is the central canal
- The gray matter has fibers in the middle (posterior gray commissure and anterior gray commissure)
- Leptomeninges (pia and arachnoid) surrounds the spine, surrounded by dura mater (the most external, thick, encircling bundle in these images)


Sensory & Motor Tracts of the Human Spinal Cord
Sensory Pathways (Ascending)
Motor Pathways (Descending)
Dorsal Column-Medial Lemniscus:
Fasciculus Gracilis
Fasciculus Cuneatus
Spinocerebellar Tracts:
Dorsal Spinocerebellar Tract
Ventral Spinocerebellar Tract
Spinothalamic Tracts (Anterolateral System):
Lateral Spinothalamic Tract
Anterior Spinothalamic Tract
Spino-olivary Fibers
Corticospinal Tracts (Pyramidal Tracts):
Anterior Corticospinal Tract
Lateral Corticospinal Tract
Rubrospinal Tract
Reticulospinal Tracts:
Lateral Reticulospinal Tract
Medial Reticulospinal Tract
Olivospinal Tract
Vestibulospinal Tract
Tectospinal Tract

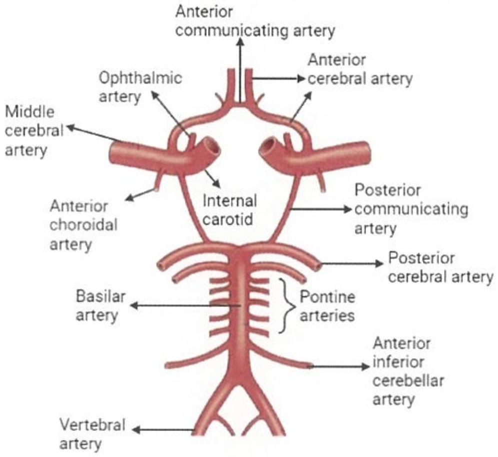
Created with BioRender


dura
arachnoid space
arachnoid
pia

Sagittal section of spine at the sacral level showing outer myelinated white matter (blue) and gray matter in the core. The meninges are nicely seen here: Pia, arachnoid, and dura. The arachnoid displays nice subarachnoid empty spaces which contain CSF



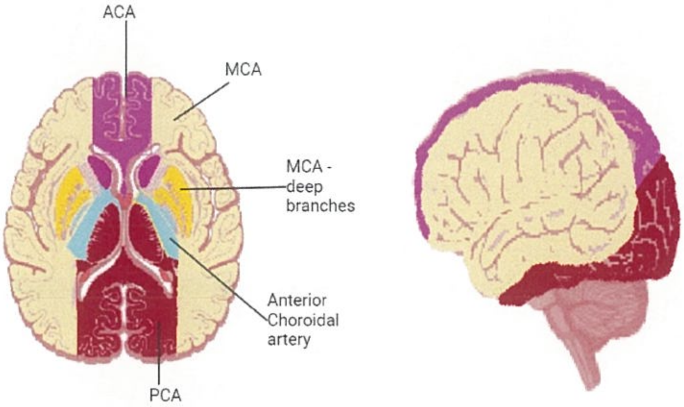
Angiogram demonstrating circle of Willis

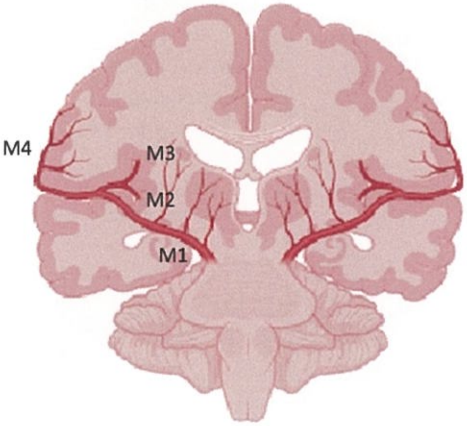

Anterior communicating artery
Anterior cerebral artery
Ophthalmic artery
Middle cerebral artery
Internal carotid
Anterior choroidal artery
Posterior communicating artery
Posterior cerebral artery
Basilar artery
Pontine arteries
Anterior inferior cerebellar artery
Vertebral artery

Schematic view of the circle of Willis, created with BioRender

CIRCLE OF WILLIS

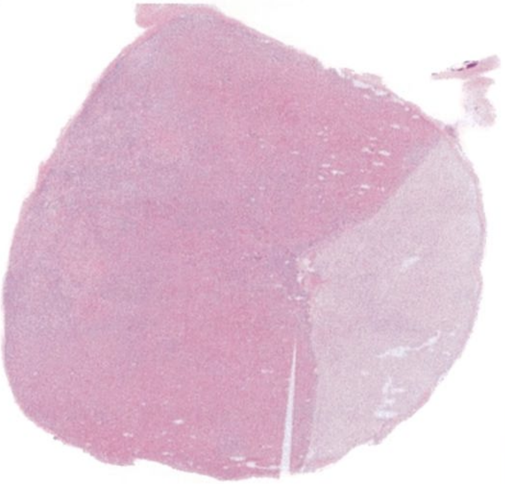
- Main arterial supply and simplified vascular territory in figure below


ACA
MCA
MCA - deep branches
Anterior Choroidal artery
PCA



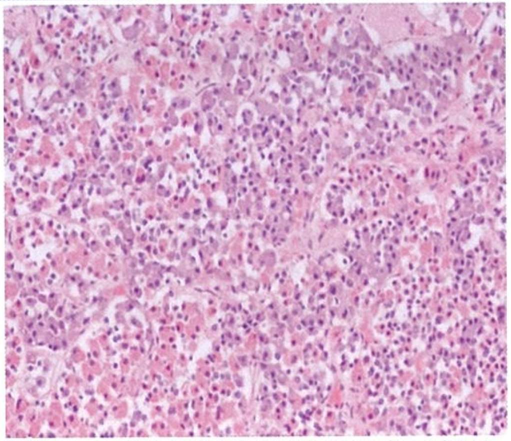
Middle cerebral artery branches: M1 sphenoidal segment, M2 insular segment, M3 opercular segment, M4 cortical segment

Created with BioRender

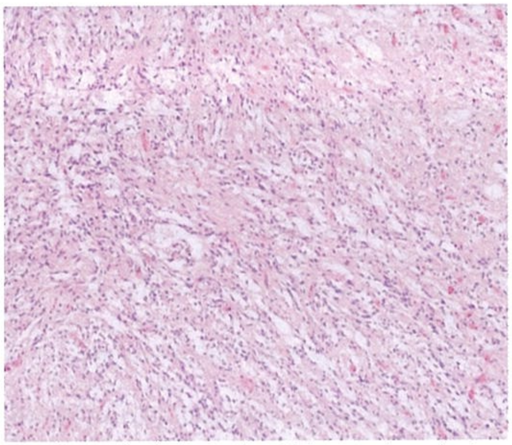


PITUITARY GLAND (ANTERIOR)

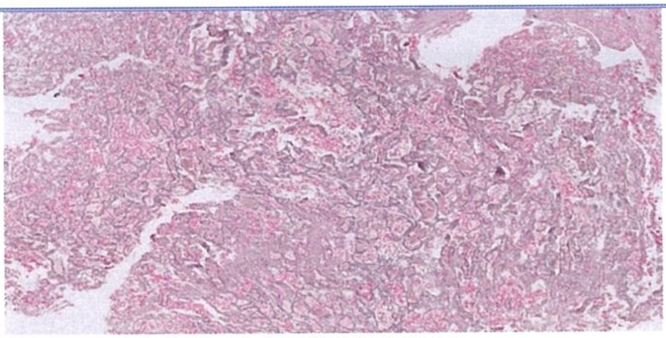
- **Adenohypophysis**
  - **Neuroendocrine cells: Acidophilic, basophilic, and chromophobic (see table below)**
  - Preserved trabeculation on reticulin stain
  - Usually positive for all hormones in a well distributed way (FSH/LH/ACTH/PROL/TSH/GH)
  - Usually positive for all transcription factors (PIT1/SF1/TPIT)
  - The portion known as pars tuberalis contains cords of epithelial cells and is filled with hypophyseal portal vessels
  - Image on the left shows H&E with low-power view of the pituitary gland, nicely demonstrating the anterior adenohypophysis (darker stain) and the posterior neurohypophysis (pale)



H&E showing high-power view of the adenohypophysis; neuroendocrine cells: Acidophilic, basophilic, and chromophobic



H&E showing high-power view of the neurohypophysis

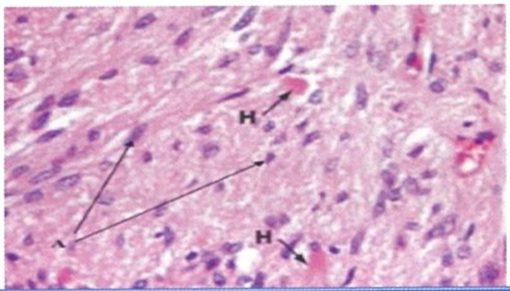


H&E showing preserved reticulin trabeculation

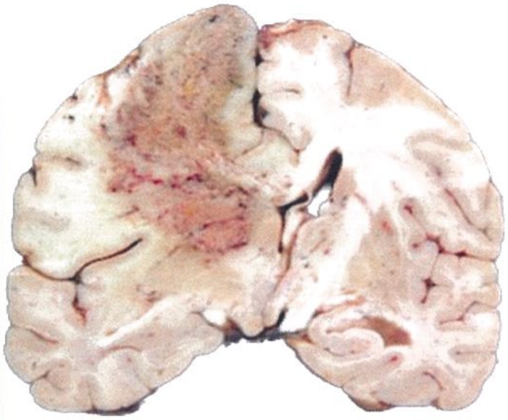
Staining	Cell Type
Basophilic	Thyrotrophs, Gonadotrophs, Corticotrophs
Acidophilic	Somatotrophs, Lactotrophs
Chromophobic	May be basophils or acidophils that have degranulated and are depleted of hormone

PITUITARY GLAND (POSTERIOR)

- Neurohypophysis
  - ➢ It is composed of the axons of hypothalamic neurons
  - ➢ It also forms the pituitary stalk
  - ➢ Oxytocin and antidiuretic hormone (ADH)
  - ➢ Herring bodies (H) and pituicytes (A) in the H&E below help to identify the neurohypophysis



EDEMA



Gross picture showing a glioblastoma with vasogenic edema
Picture courtesy: Anthony Yachnis, MD

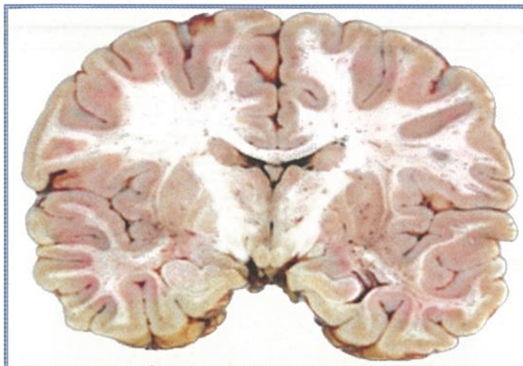
VASOGENIC CEREBRAL EDEMA

MORPHOLOGY

- The associated angiogenesis with microvascular proliferation and poorly formed BBB results in vasogenic edema and mass effect
- Gray-white matter differentiation is maintained
- The edema involves mainly white matter, extending in a finger-like fashion
- Secondary effects of vasogenic edema are similar to cytotoxic edema, with effacement of cerebral sulci, with or without midline shift

OTHER HIGH YIELD POINTS

- Vasogenic edema results from BBB breakdown allowing fluid and proteins to cross from the intravascular compartment to the extracellular CNS spaces
- Usually happens with: Trauma, hemorrhage, infection, tumors with extensive angiogenesis
- Extracellular fluid accumulation with pallor of staining is seen when there is hypoxia
- MRI: Hyperintense T2 and FLAIR signals, which do not show restricted diffusion



Gross picture showing gray matter edema consistent with cytotoxic edema
Picture courtesy: Anthony Yachnis, MD

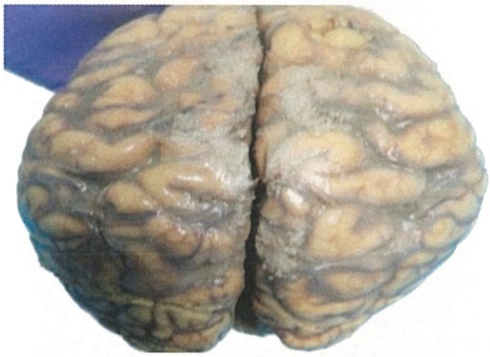
CYTOTOXIC CEREBRAL EDEMA

MORPHOLOGY

- Diffuse brain swelling from hypoxia
- Histologic effects of acute hypoxia: Cytoplasmic eosinophilia and nuclear pyknosis
- Widening of the gyri and compression of the ventricles
- Swelling of neurons primarily affecting the gray matter

OTHER HIGH YIELD POINTS

- Hypoxia promotes loss of ATP and impaired function of the Na+/K+ ATPase
- The influx of Na+ and water intracellularly results in swelling of neurons
- Many pathologic processes have components of vasogenic and cytotoxic edema (such as a hemorrhagic cerebral infarct)
- MRI: As cells swell due to inward shift of water, there is a commensurate decrease in diffusion, identified as high signal on DWI



Gross picture displaying congested vasculature

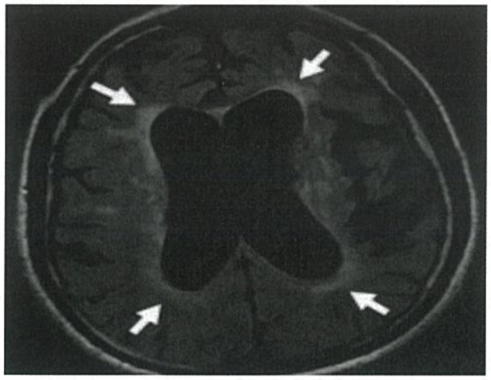
CONGESTIVE CEREBRAL EDEMA

MORPHOLOGY

- Increase in intravascular pressure
- Increase in cerebrovascular resistance and filling of capillary beds
- Accumulation of fluid over time can be diffuse

OTHER HIGH YIELD POINTS

- Cerebral edema can lead to herniation (headache, nausea, vomiting)
- Altered state of consciousness or coma and focal neurologic deficits may occur



INTERSTITIAL CEREBRAL EDEMA

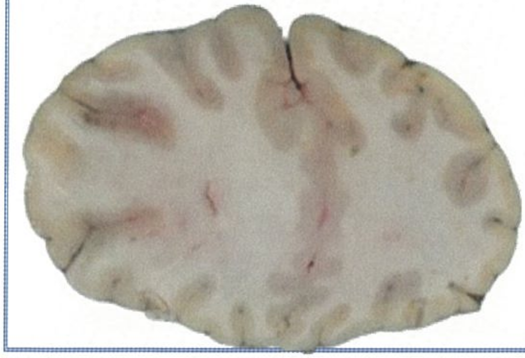
MORPHOLOGY

- Increase in intraventricular volume
- Transependymal fluid shifts
- Accumulation in the periventricular white matter

OTHER HIGH YIELD POINTS

- Radiology: Arrows (image on left) indicate the transependymal fluid shift

HERNIATION SYNDROMES



CINGULATE GYRUS/SUBFALCINE HERNIATION

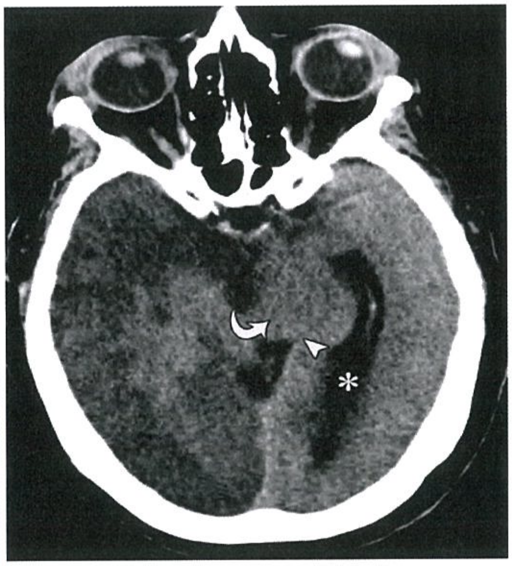
MORPHOLOGY

- Caused by a unilateral frontal lesion with mass effect
- Also typically with ipsilateral ventricular compression

OTHER HIGH YIELD POINTS

- Can lead to anterior cerebral artery compression with infarction

Image on the left is coronal section of the frontal pole showing asymmetry with midline deviation. This case had a subfalcine herniation



Radiology showing a glioblastoma with vasogenic edema and marked midbrain compression

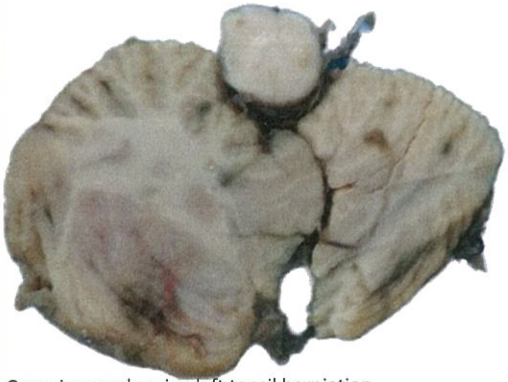
TRANSTENTORIAL HERNIATION

MORPHOLOGY

- **The uncus and parahippocampal gyrus show pronounced groove**
- They herniate around the tentorium cerebelli
- Marked compression of the midbrain
- Obliteration of suprasellar cistern

OTHER HIGH YIELD POINTS

- **CNIII compression** leading to a fixed, dilated pupil
- Brainstem compression by herniating temporal lobe often accompanied by secondary hemorrhagic lesion in midbrain and pons (Duret hemorrhages)
- **Kernohan notch:** Compression of the brainstem against the tentorial edge in the opposite direction of the herniation can cause false localization of motor deficit
- Displacement and eventual occlusion of the posterior cerebral artery may lead to occipital lobe infarction



Gross image showing left tonsil herniation

CEREBELLAR TONSILLAR HERNIATION

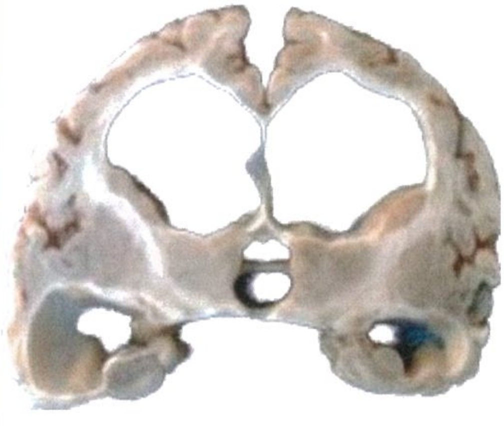
MORPHOLOGY

- **Cerebellar tonsils are compressed through the foramen magnum**
- The tonsils are discolored and compressing the caudal medulla
- Secondary to posterior fossa mass effect

OTHER HIGH YIELD POINTS

- Often leads to necrosis of the herniated structures
- Can lead to respiratory and cardiac arrest from brainstem compression

HYDROCEPHALUS



Gross image showing bilateral lateral ventricle and 3rd ventricle dilation
Picture courtesy: Anthony Yachnis, MD

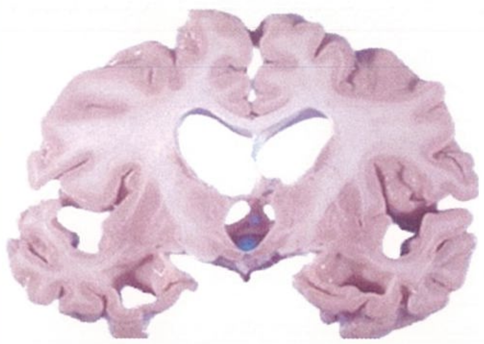
HYDROCEPHALUS

MORPHOLOGY

- **Marked dilation of the ventricles above the level of obstruction**
- Lateral ventricles and 3rd ventricle dilation is shown in the image on the left
- This can be caused by an obstruction in the aqueduct of Sylvius

OTHER HIGH YIELD POINTS

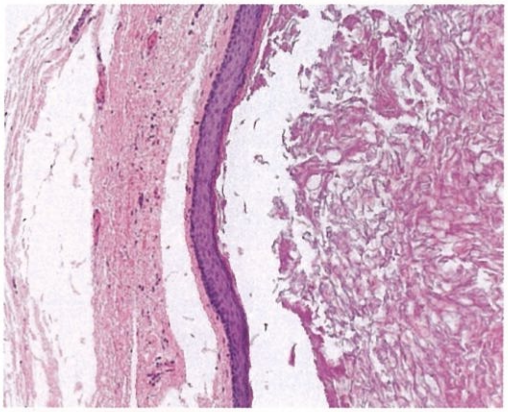
- Common sites of obstruction (foramens of Monro, Luschka, and Magendie, as well as the aqueduct of Sylvius)
- Congenital causes: Aqueductal stenosis, atresia, agenesis; Arnold-Chiari malformation, Dandy-Walker, and neural tube defects
- Acquired causes: Obstruction by infectious, inflammatory, hemorrhagic (germinal matrix, ventricular hemorrhage), traumatic, or neoplastic causes
- Rarely caused by overproduction of CSF (choroid plexus papilloma), failure of CSF absorption (arachnoid granulations), and dural sinus thrombosis
- Differential: Hydrocephalus ex vacuo



HYDROCEPHALUS EX VACUO

- **Compensatory ventricular enlargement**
- Response to parenchymal loss in neurodegenerative processes
- Usually no increase in CSF pressure
- Often increased proportional to the level of brain atrophy

BENIGN CYSTS



H&E showing keratin debris and a squamous lining

EPIDERMOID CYST

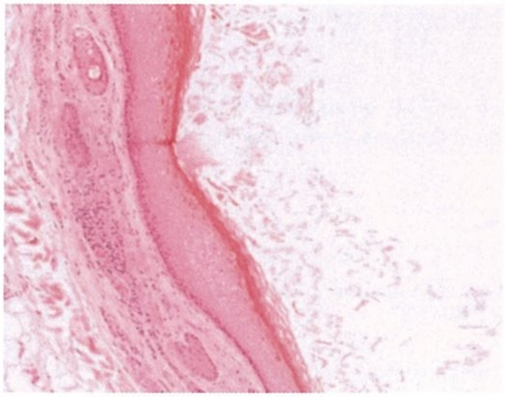
MORPHOLOGY

- Simple stratified squamous epithelium with no adnexal structures
- Keratinous debris
- Might have foreign body giant cell reaction from ruptured cyst
- Rare progression to squamous carcinoma

OTHER HIGH YIELD POINTS

- Epidermoid cyst more common than dermoid cyst
- Bright on diffusion-weighted images
- Typically do not enhance

Path Presenter



H&E showing adnexa and epithelial lining

DERMOID CYST

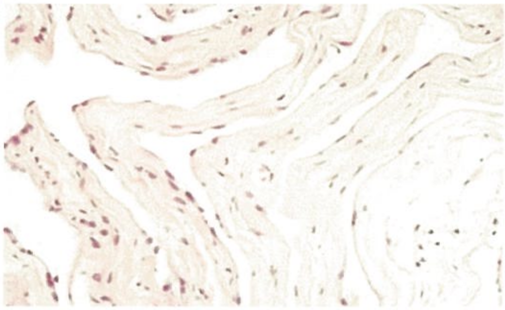
MORPHOLOGY

- Stratified squamous epithelium with adnexal structures
- Macroscopic: “Cheesy” keratinous contents; matted hair; sinus tract
- More often midline, posterior fossa
- Occasional osseous metaplasia
- Mitoses absent/rare

OTHER HIGH YIELD POINTS

- Usually in children
- Rare progression to squamous cell carcinoma

Path Presenter



H&E showing ependymal cyst, no basal lamina

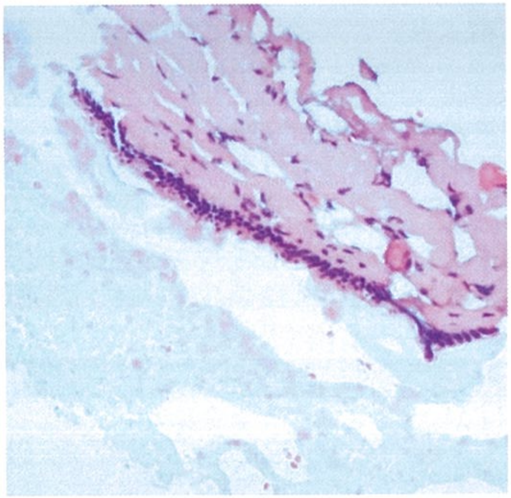
EPENDYMAL/GLIOEPENDYMAL CYST

MORPHOLOGY

- Simple cuboidal cells, no fibrous capsule
- Lacks cilia
- Cells rests on neuropil without basal lamina
- Usually intracranial but may affect the spinal cord
- No communication with ventricles

OTHER HIGH YIELD POINTS

- Differential diagnosis: Endodermal cyst
- IHC: (+) S100, GFAP; EMA and cytokeratin variable



H&E showing pseudostratified epithelium and amorphous, proteinaceous cyst contents

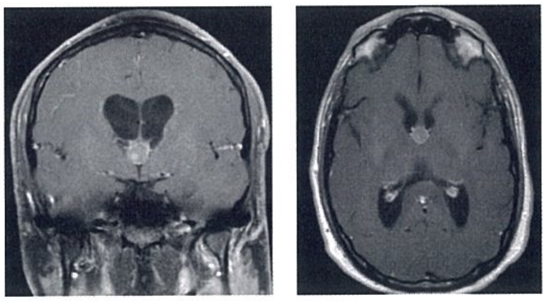
COLLOID CYST

MORPHOLOGY

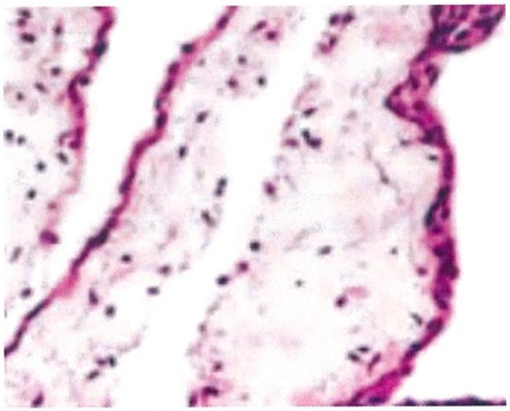
- Pseudostratified epithelium with both ciliated and goblet cells
- Cuboidal or flattened with pressure atrophy
- Amorphous, proteinaceous material
- May have xanthogranulomatous reaction
- Cyst wall often with reactive cells

OTHER HIGH YIELD POINTS

- 3rd ventricle (almost/always)
- **IHC: EMA uniformly positive; (-) S100**
- Radiology: FLAIR hyperintense cyst
- Differential diagnosis: Arachnoid cyst, Rathke's cleft cyst



Colloid cyst radiology
Picture courtesy: Dr. Timothy Richardson



H&E showing cyst lining formed by meningothelial cells

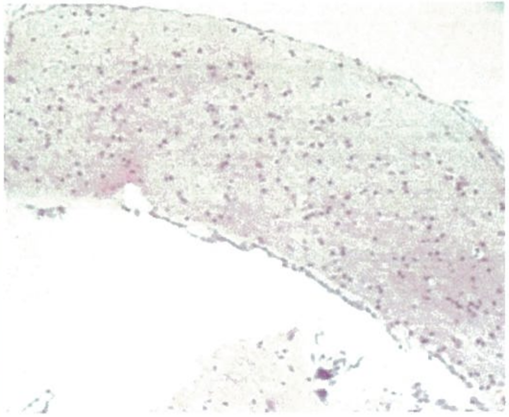
ARACHNOID CYST (MENINGEAL CYST)

MORPHOLOGY

- Lined by a single layer of mature arachnoid cells, meningothelial cells; filled with CSF
- Rare foci of meningothelial hyperplasia
- Cyst wall may show an outer fibrotic or collagenous layer

OTHER HIGH YIELD POINTS

- Mostly congenital
- IHC: (+) EMA (in the cyst lining); (-) GFAP, synaptophysin, S100
- Differential diagnosis: Epidermoid cyst, endodermal cyst, ependymal cyst



H&E showing cyst lining formed by simple columnar epithelium

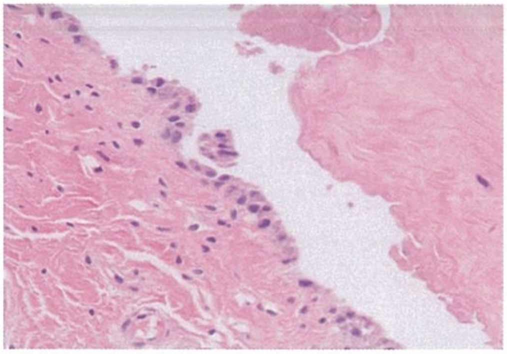
ENDODERMAL CYST/NEUROENTERIC CYST

MORPHOLOGY

- Lined by simple columnar epithelium with or without cilia
- Can be complex, similar to respiratory epithelium, even with muscularis mucosa

OTHER HIGH YIELD POINTS

- Intraspinal (intradural extramedullary) most common location
- Posterior fossa most common intracranial site
- Malignant transformation is rare
- IHC: (+) EMA, cytokeratin, CEA (in some cases); (-) GFAP
- Differential diagnosis: Ependymal cyst, colloid cyst



H&E showing synovial cells forming the cyst lining

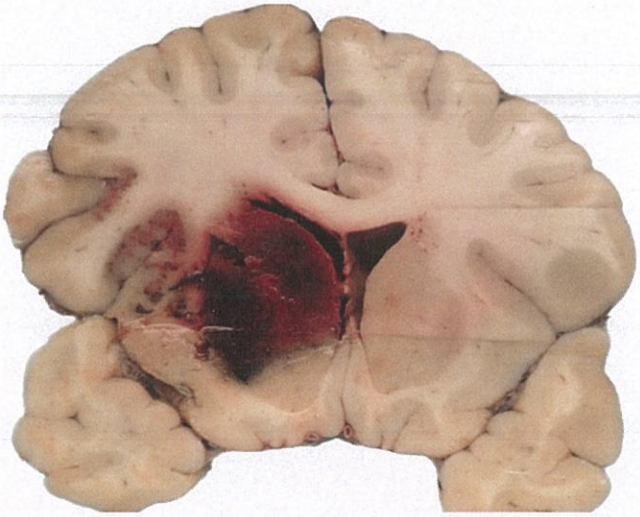
FACET JOINT SYNOVIAL CYST

MORPHOLOGY

- Lumen lined by synovial epithelium but not always present
- Surrounding reactive changes
- Associated calcium pyrophosphate deposition can happen

OTHER HIGH YIELD POINTS

- Degeneration of the facet joint leads to fluid escape from the joint capsule within the synovium, creating a sac-like protrusion

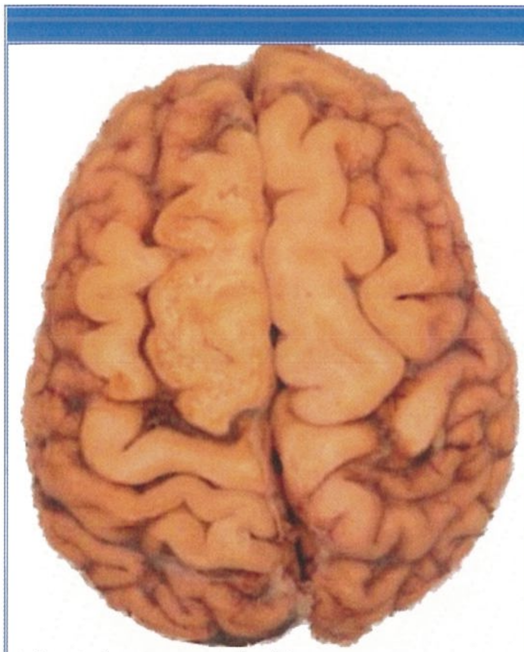


CEREBROVASCULAR DISEASES

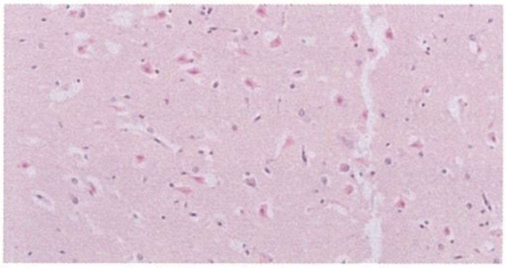
KATHERINE E. SCHWETYE, MD, PhD
RAQUEL T. YOKODA, MD

2. CEREBROVASCULAR DISEASE

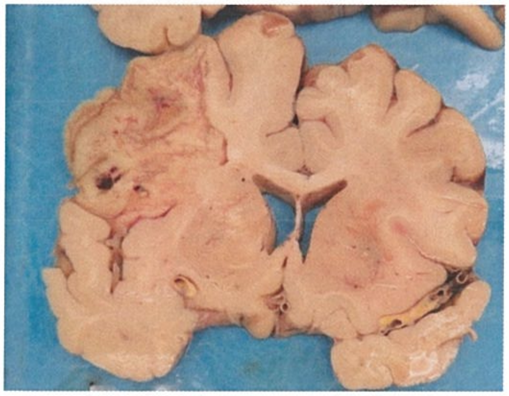
STROKES



Ischemic changes seen in the left ACA territory
Subacute: Antemortem interval of 6 days



Acute neuronal cell change showing vacuolated background, red neurons, and no macrophages



Infarct changes in the left MCA, M1 territory
Subacute to chronic: Antemortem interval 1 week

STROKES

MORPHOLOGY

- Acute ischemic stroke/infarct → cytotoxic edema (cells swell)
- Tissue in the area expands → mass effect and herniation can occur
- An infarct occurring 5-8 hours before death may not be visible grossly or histologically
- Changes develop over 12-36 hours
- Grossly edematous, soft, and necrotic
- Microscopically 1-4 days: Red neurons and rarefaction/vacuolization of the parenchyma

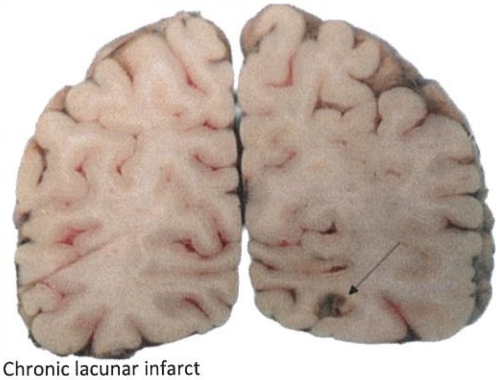
OTHER HIGH YIELD POINTS

- The 3rd most common cause of death (150,000 deaths per year)
- In 2021, 1 in 6 deaths from cardiovascular disease was due to stroke
- About 795,000 cases diagnosed each year in the U.S.
  - ➢ 20% of these patients die within 3 months
  - ➢ 25% recover completely
  - ➢ 55% recover with some level of disability
- In the U.S., approximately 4 million people are stroke survivors
- **Stroke is the leading cause of long-term disability**
- About 25% of strokes occur in an individual with a previous stroke
- Important risk factors for stroke: Hypertension, diabetes, hyperlipidemia, cardiac disease, atrial fibrillation, tobacco use, oral contraceptives, prior history of strokes or transient ischemic attacks
- The nervous system is very sensitive to deprivation of oxygen and glucose
  - ➢ Irreversible damage begins soon after hypoxia or hypoglycemia
  - ➢ Ischemic brain damage is related to hypoxia
  - ➢ Hypoxia can occur without ischemia, but this usually does not cause necrosis
  - ➢ Recovery is better after hypoxemic hypoxia than after global ischemia
  - ➢ **87% of all strokes are ischemic strokes**
- Injury following hypoxia or ischemia will depend on:
  - ➢ The severity and duration of the insult
  - ➢ CNS temperature (low temperature is protective)
  - ➢ Blood glucose level (high levels associated with poor outcomes)
  - ➢ Severity of the swelling can occlude the circulation to the brain and brainstem

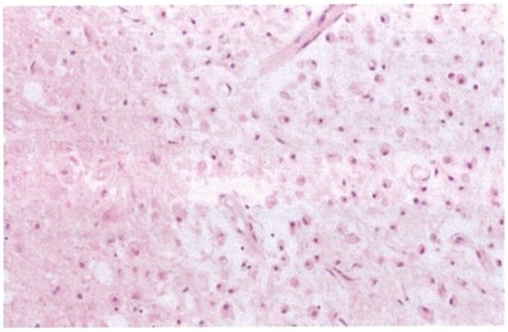
ANOXIA AND HYPOXIA

MORPHOLOGY

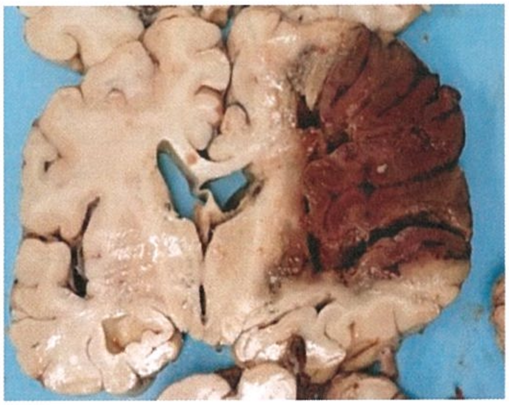
- Watershed (border zone) infarction at vulnerable end-artery regions
  - ➢ Sommer's sector (CA1)
  - ➢ Purkinje cells
  - ➢ Cerebral cortex
- **6-8 hours → no changes**
- First noticeable change is mild loss (blurring) of gray-white junction
- **Acute changes** (12-24 hours after hypoxia):
  - ➢ Gross: Brain swelling, dusky discoloration; if large, can lead to mass effect and herniation
  - ➢ Histology: Areas of pallor, acute neuronal cell eosinophilic change (red-dead), and pyknotic nuclei
- **Subacute changes** (2-4 days):
  - ➢ Gross: Cracking of the tissue at the junction of infarcted and non-infarcted areas
  - ➢ Histology: Macrophages and microglia after 3-5 days, capillary proliferation, loss of axons within the lesion (can be demonstrated by neurofilament stain)
- **Chronic changes** (1-2 weeks):



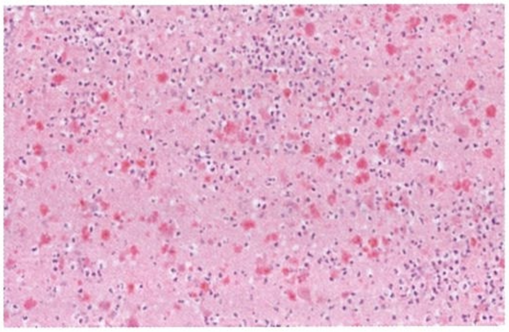
Chronic lacunar infarct



Chronic infarct, macrophage-rich



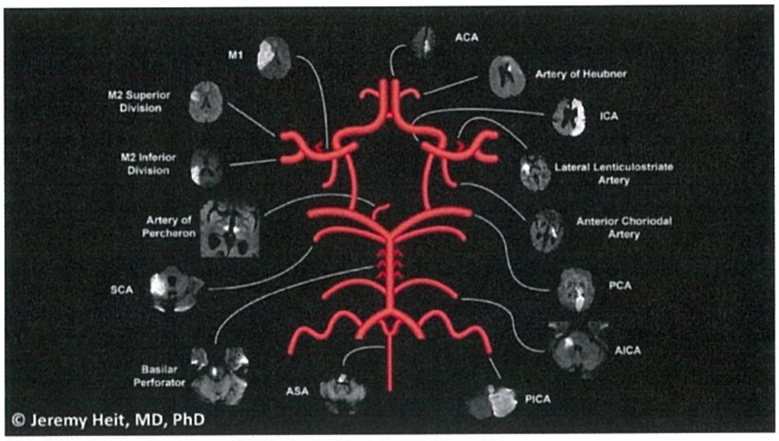
Reperfusion necrosis at the MCA territory



Extensive necrosis and hemorrhage in the reperfused infarct

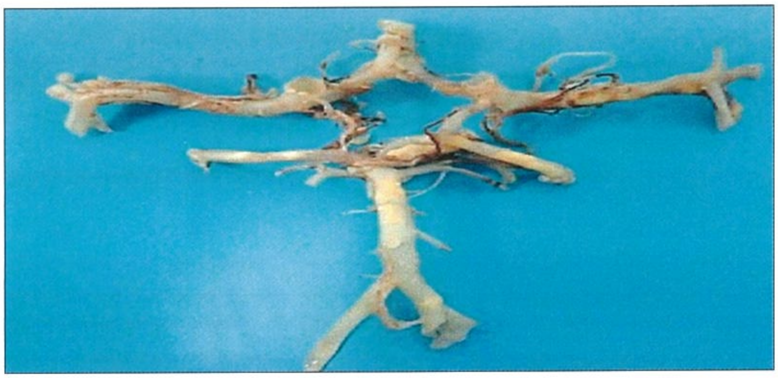
- Gross: Liquefactive necrosis, cavitation
- Histology: Macrophages persist until the necrotic tissue is absorbed
- **Remote infarct** (months to years):
  - Gross, cystic lesion and tissue is retracted/lost
  - Histology: Well-formed glial scar, no macrophages, rim of scar shows reactive astrocytes, gliosis

Correlation with radiology and arterial territory
Picture courtesy: Jeremy Heit, MD, PhD


ACA
M1
Artery of Heubner
M2 Superior Division
ICA
M2 Inferior Division
Lateral Lenticulostriate Artery
Artery of Percheron
Anterior Choriodal Artery
SCA
PCA
AICA
Basilar Perforator
ASA
PICA

© Jeremy Heit, MD, PhD

- If reperfusion after an embolic infarct → hemorrhagic areas of necrosis
- Embolic infarcts
- Circle of Willis evaluation of atherosclerosis (mild/moderate/severe)

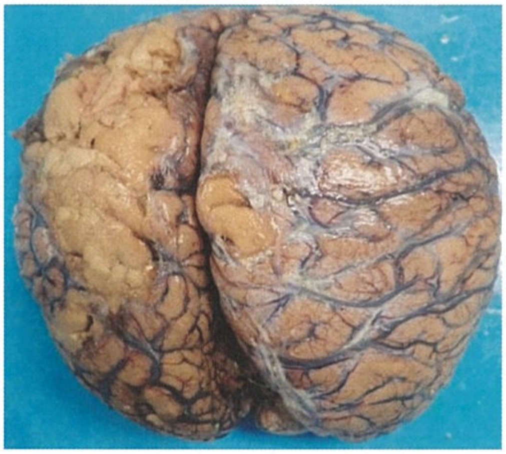


- Radiology → CT scan and MRI with diffusion-weighted image (DWI) are the best for detecting ischemic lesions

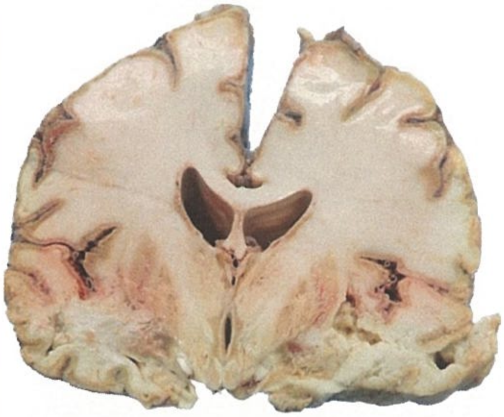
OTHER HIGH YIELD POINTS

- Differential diagnosis:
  - Active demyelination
  - Glioma
  - Brain hemorrhage

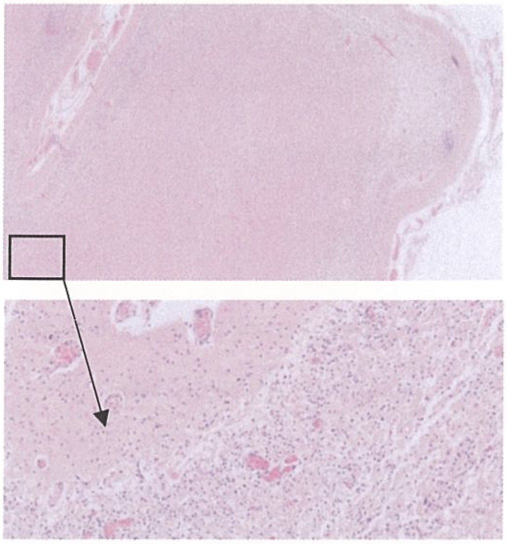
Swollen, congested brain characteristic of global anoxic injury



Global anoxic injury. Atrophy of the entire cortical ribbon with brownish discoloration and separation of the underlying white matter ("orange peel")



Pseudolaminar necrosis or cortical laminar necrosis; gliotic cortex with underlying sheets of macrophages



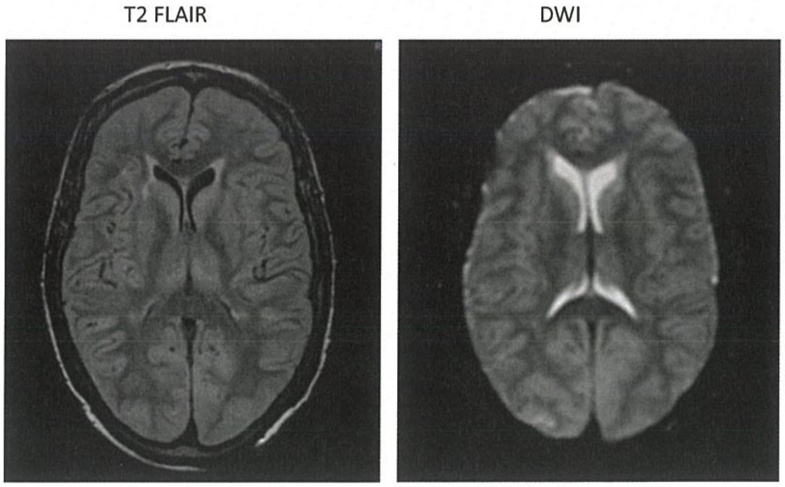
GLOBAL ANOXIC INJURY

MORPHOLOGY

- Hypoxic-ischemic encephalopathy (HIE) → neuronal loss, pseudolaminar necrosis, white matter degeneration
- Pseudolaminar necrosis: Usually the damage is greater in the deep sulci

OTHER HIGH YIELD POINTS

- Affects the brain globally
- The brain receives 750 mL/min or 15% of the cardiac output
- Conditions that lower the brain's blood flow dramatically can lead to global hypoxia, anoxia, and brain death
- Cerebral perfusion pressure (CPP) ranges from 60-160 mmHg
- CPP = mean arterial pressure (MAP) – intracranial pressure (ICP)
- In adults without hypertension, arterioles and arteries can autoregulate to maintain a cerebral blood flow (CBF) of 50-55 mL/100g/min
- If CPP < 60mmHg → hypoxia can occur
- If CPP > 160 mmHg → hypertensive encephalopathy can occur
- Oxygen demand adjusts CBF if PO2 falls < 50 mmHg
- Hypoxia can increase CBF by 400%
- Chronic hypoperfusion → cerebral edema
- CO2 retention/inhalation can increase CBF
- Patients with cardiogenic or hypovolemic shock, status post cardiac arrest
- The brain can adapt to slowly developing hypoxia, but acute HIE beyond energy failure adds lactic acid and other toxic metabolites to the circulation that can directly cause neuronal damage
- Respirator brain = non-perfused brain
- Consequences of HIE
    - ➢ HIE → diffuse cortical and thalamic neuronal loss with intact brainstem → persistent vegetative state
    - ➢ HIE→ loss of cerebral and brainstem function → brain death
- Radiology: Diffuse changes of the cerebral cortex with increased DWI signal, suggesting bilateral ischemic change after cardiac arrest



2. CEREBROVASCULAR DISEASE

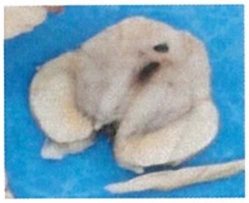
DURET HEMORRHAGE

MORPHOLOGY

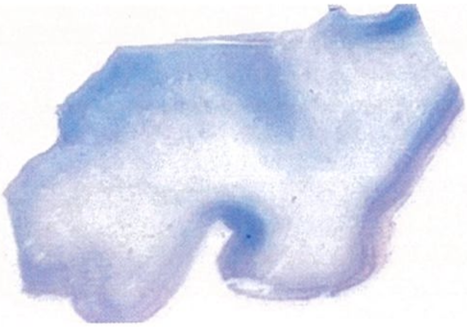
- Often visible grossly as a brown stain in the midbrain

OTHER HIGH YIELD POINTS

- Hemorrhage in the midbrain or pons due to transtentorial herniation
- From tearing branches of basilar artery



LBF staining at 1x showing myelin pallor restricted to the white matter



Picture courtesy: Timothy Richardson, DO, PhD

SUBCORTICAL LEUKOENCEPHALOPATHY, BINSWANGER TYPE

MORPHOLOGY

- Myelin pallor and arteriolosclerosis, sometimes infarct
- Several lesions, lacunar infarcts, hypertension-related
- Historically restricted to white matter
  - ➢ Changes may be focal or widespread
  - ➢ White matter pallor, edema, variable gliosis
  - ➢ Cerebral cortex is preserved

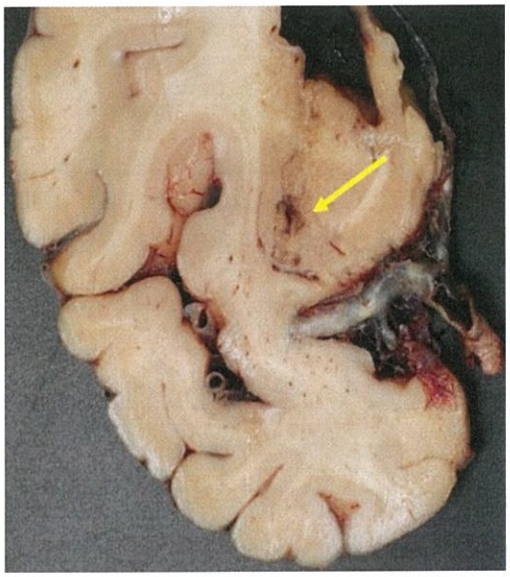
OTHER HIGH YIELD POINTS

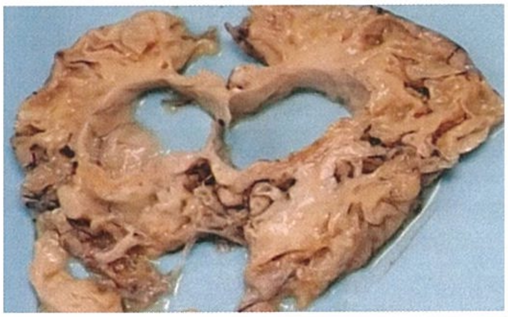
- Particular form of vascular-related dementia
- Most pathologists' diagnoses of this entity are now under the umbrella term "hypertensive cerebrovascular disease"

Several subcentimeter lacunar infarcts

Picture courtesy: Jamie Walker, MD, PhD

Multiple advanced infarcts; patient survived years in vegetative state

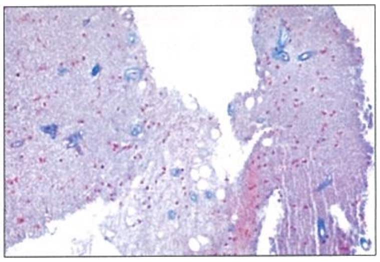


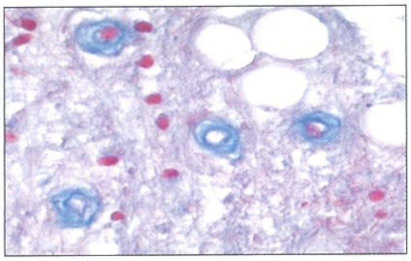


HYPERTENSIVE CEREBROVASCULAR DISEASE

MORPHOLOGY

- Several lesions, lacunar infarcts, usually small, subcentimeter
- Atherosclerosis and arteriolosclerosis
- Widening of perivascular spaces
- Fibrosis of the vessel wall (Trichrome-Mason)
- Over time → liquefactive necrosis and a slit-like cavity filled with fluid in chronic/remote infarcts
- Trichrome highlights sclerosis in the vessel walls
- Arteriolosclerosis: Concentric laminated thickening (onion-skinning)

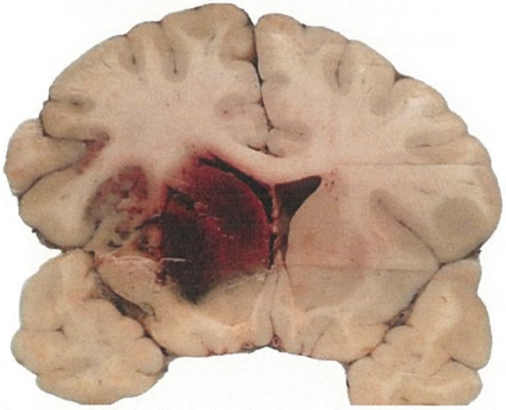


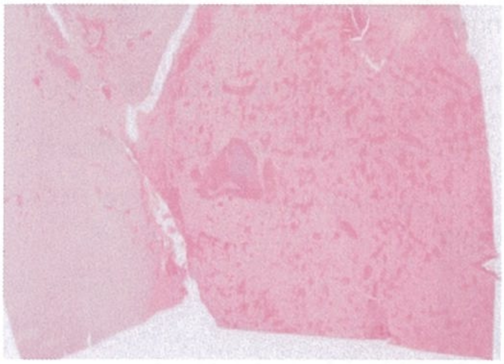


OTHER HIGH YIELD POINTS

- Basal ganglia hemorrhage highly associated with HTN
- Deep cerebral white matter
- Thalamus
  - ➢ 20% of all strokes
  - ➢ Associated with hypertension
  - ➢ Increased risk with age
  - ➢ Accumulation of lacunar infarcts can decrease mental activity (multi-infarct dementia, vegetative states)
  - ➢ Bright signal MRI T2 and FLAIR in the white matter and deep nuclei
- Differential diagnosis: CADASIL

2. CEREBROVASCULAR DISEASE


Basal ganglia hemorrhage


Low power from the lesion above

HYPERTENSIVE CEREBROVASCULAR DISEASE WITH SPONTANEOUS INTRACEREBRAL HEMORRHAGE (ICH)

MORPHOLOGY

- Gross: Fresh or recently clotted blood; edema and herniation can occur
- Histology: Large-caliber vessels surrounding brain hemorrhage show atherosclerotic and arteriolosclerotic disease; can have fibrinoid necrosis

OTHER HIGH YIELD POINTS

- 15-20% of all strokes
- Peak incidence: 60 years old
- Occurs along the lenticulostriate branches of the MCA
- Can happen along the pontine perforators of the basilar artery
- Most often in the deep nuclei
- < 10 mL with higher survival rates
- > 60 mL with poor prognosis

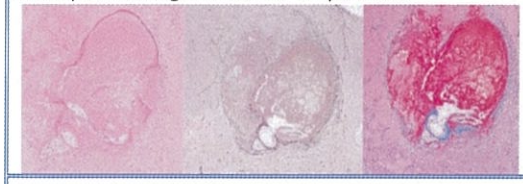
HYPERTENSIVE CEREBROVASCULAR DISEASE – POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) OR REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME (RPLS)

MORPHOLOGY

- Can grossly range from old infarcts to hemorrhagic infarcts in the posterior circulation
- Histology is poorly specific

OTHER HIGH YIELD POINTS

- Severe increase in blood pressure
- Can occur at any age; equally prevalent in males and females
- MRI shows increased T2 signal posteriorly in the parieto-occipital white matter; DWI variable on restriction to the white matter
- Differential diagnosis includes PCA infarct and encephalitis/vasculitis


H&E, reticulin, and trichrome showing the ruptured aneurysm and original vessel in the putamen

CHARCOT-BOUCHARD ANEURYSM

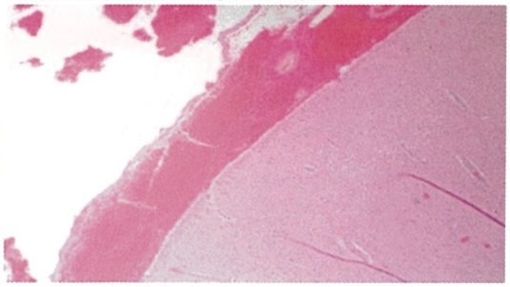
MORPHOLOGY AND OTHER HIGH YIELD POINTS

- Occurs in small penetrating vessels < 300 micrometers in diameter
- Often in the lenticulostriate vessels of the basal ganglia
- Associated with chronic hypertension
- Common cause of cerebral hemorrhage

Emboli Material	Clinical Correlation
Infective	Bacterial endocarditis
Fat	Long bone fracture
Air	Cardiac bypass surgery
Foreign body	Intravenous drug users

ISCHEMIC STROKE FROM EMBOLIC SOURCE

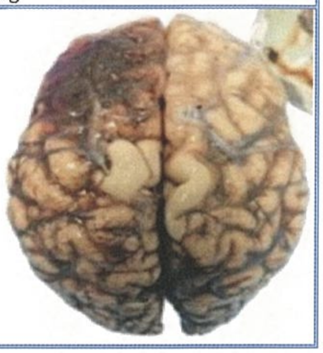
- Clinical scenarios:
  - Thrombus in the left atrium in a patient with atrial fibrillation
  - Thrombus in the left ventricle after myocardial infarction
  - Vegetations on the cardiac valves (bacterial endocarditis)
  - Ulcerative atherosclerosis of the common and internal carotid arteries
  - Paradoxical emboli due to right to left shunting


Subarachnoid hemorrhage at low power

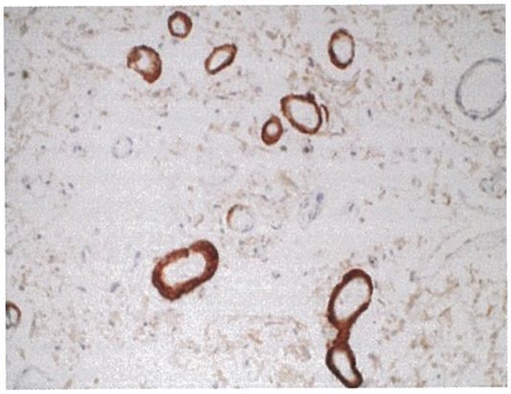
SUBARACHNOID HEMORRHAGE

HIGH YIELD POINTS

- Can result in seizures and sudden death
- May occur in trauma or due to spontaneous rupture of a berry aneurysm



Amyloid staining (10D5) of cerebral amyloid angiopathy showing blood vessels



CEREBRAL AMYLOID ANGIOPATHY

MORPHOLOGY

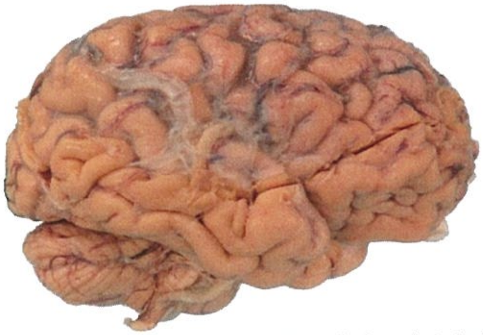
- Hyalinized blood vessels with mural thickening by eosinophilic amorphous material; late stage with "double-barrel" contour

OTHER HIGH YIELD POINTS

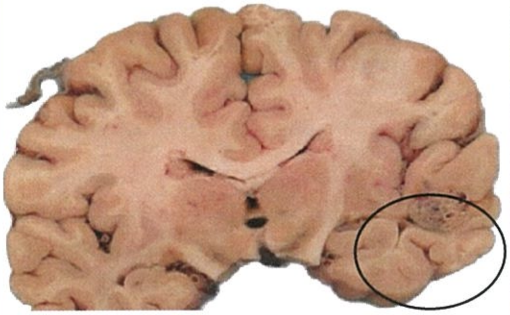
- Vasculopathy arising from Aβ-amyloid peptide within vessel walls
- Can affect leptomeningeal vessels and superficial cortical blood vessels
- Can lead to lobar hemorrhages
- Affects large portion of Alzheimer disease patients with peak incidence at age 70-80
- **Some patients can develop Aβ-related angiitis (ABRA)** – vasculitis (fibrinoid necrosis)
- Rare genetic forms: Transthyretin, gelsolin, cystatin C, and prion protein accumulation
- Differential diagnosis includes primary angiitis of the central nervous system (PACNS) vs. hypertensive vasculopathy/arteriolosclerosis

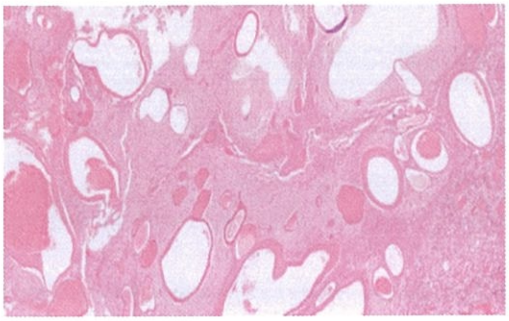
VASCULAR MALFORMATIONS

Arteriovenous malformation (AVM) on the surface



Coronal section shows a compact "mass" of tangled, thick-walled blood vessels (nidus)



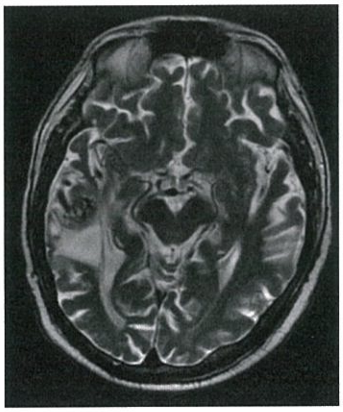


Cluster of abnormal vessels with intervening glial tissue

ARTERIOVENOUS MALFORMATIONS

MORPHOLOGY

- Thick-walled arteries have smooth muscle proliferation, collagen deposition, and reduplication of the internal elastic membrane
- Abnormal blood vessels can show recanalization, thrombosis, or evidence of previous embolization
- By definition, AVM has intervening gliotic brain tissue



MRI from the same autopsy case as shown in left column: A tangle of vessels seen in the right temporal lobe

OTHER HIGH YIELD POINTS

- Congenital lesions, slight male predominance, prevalence 0.15%
- Average age at diagnosis approximately 33 years old
- Can occur in Osler-Weber-Rendu syndrome, craniofacial arteriovenous metameric syndromes, and Wyburn-Mason syndrome
- Majority supratentorial
- Lesions may be treated with radiosurgery, embolization, resection
- There is a pre-surgical grading system to help predict surgical outcome (Spetzler-Martin grading system)
- Superficial AVMs correlate with dilated veins draining from the cerebral surface
- Deep AVMs correlate with drainage into the deep venous system
- Differential diagnosis includes cavernous angioma, vascular neoplasm, and normal subarachnoid vessels

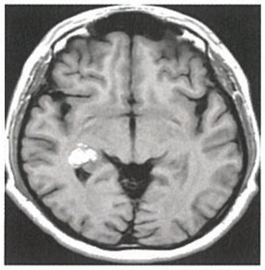
CAVERNOUS ANGIOMA

MORPHOLOGY

- Majority supratentorial, size 1-4 cm, rare in the brainstem or spinal cord
- Gross: Circumscribed hemorrhagic-appearing lesion; lobulated and purplish
- Histology: Mass of dilated, thin-walled vessels with no intervening parenchyma, vessels can be calcified or thrombosed, and surrounding brain tissue is gliotic with hemosiderin

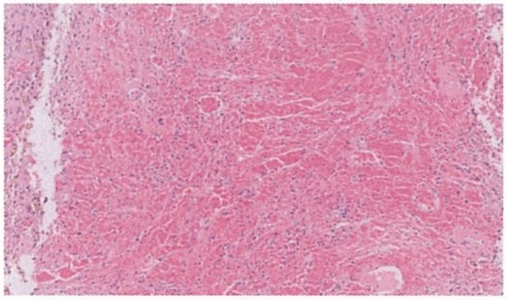
OTHER HIGH YIELD POINTS

- Prevalence 0.1%, usually solitary, slight male predominance
- Age at diagnosis 30-40 years old
- If multiple cavernous angiomas are seen, it may indicate underlying multiple cavernous malformation syndrome (autosomal dominant), mutations on chromosome 7 (CCM1, CCM2 genes), or mutations on chromosome 3 (CCM3 gene)
- Differential diagnosis includes:
  - ➢ Hemorrhagic tumor
  - ➢ Arteriovenous malformation

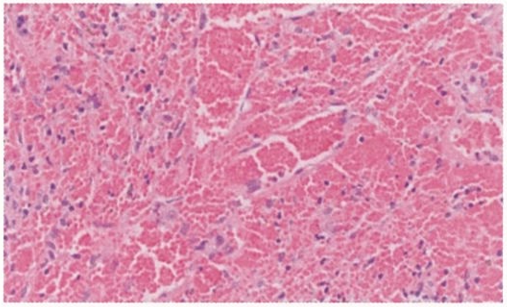


T2 MRI: Popcorn appearance is pathognomonic

Cavernous angioma, thin-walled and closely packed, with little stroma and no intervening neuroglial tissue



Cavernous angioma, high-power view



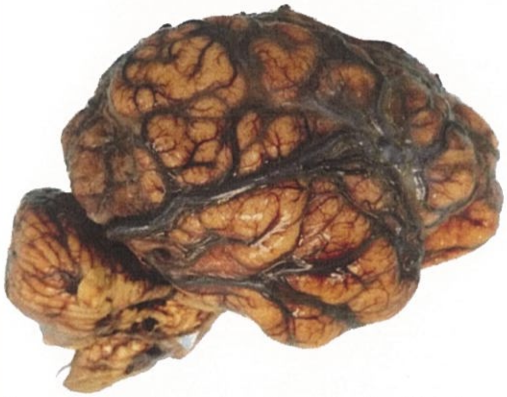
VENOUS ANGIOMA

MORPHOLOGY

- Gross: Venous caput medusae
- Resembles varicose veins

OTHER HIGH YIELD POINTS

- Congenital venous malformation: Dilated veins, fully functional veins
- Synonymous: Developmental venous anomaly (DVA)
- Prevalence 2% (account for 60% of all CNS vascular malformations)
- Can be asymptomatic
- Differential diagnosis includes dural venous thrombosis with collateral drainage



Venous angioma in an autopsy brain showing dilated veins

ANEURYSMS

INFECTIOUS ("MYCOTIC") ANEURYSMS

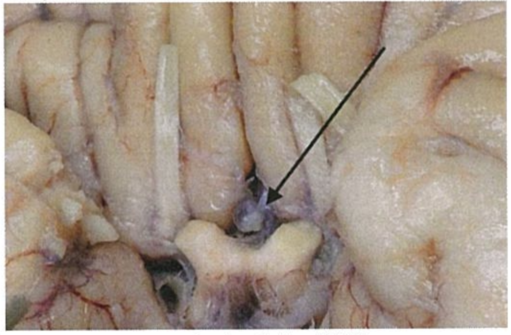
MORPHOLOGY

- Infectious organisms invade the vessel wall
- Vessel dilation
- Endothelial surface may have vegetations

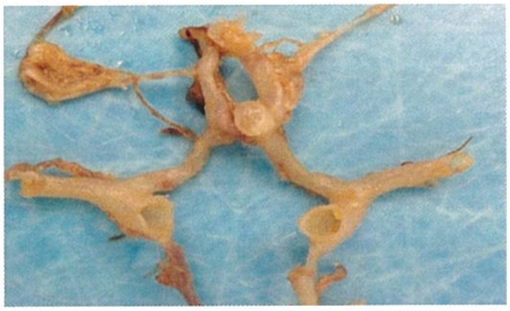
OTHER HIGH YIELD POINTS

- Can occur due to:
  - ➢ Fungus
  - ➢ Bacteria
  - ➢ Mycobacteria
- Trauma, endocarditis, meningitis, and immunosuppressed state are risk factors
- Symptoms progress rapidly and include headache, fever, and loss of consciousness
- High mortality rates
  - ➢ 90% for fungus
  - ➢ 30% for bacteria
- **Angiography is the gold standard imaging**
- Differential diagnosis:
  - ➢ Saccular aneurysm
  - ➢ Fusiform aneurysm

Berry aneurysm seen from the ventral brain



Berry aneurysm seen in the Circle of Willis



SACCULAR "BERRY" ANEURYSMS

MORPHOLOGY

- Dilation or ballooning of the cerebral artery
- Lack internal elastic lamina; disrupted muscular layer with myointimal hyperplasia

OTHER HIGH YIELD POINTS

- Prevalence 0.2% to 5%, female predominance
- 80-90% in the anterior carotid circulation with anterior communicating artery, posterior communicating artery, and middle cerebral artery
- 15% of patients may have multiple aneurysms
- Treatment of choice is coiling
- Related to subarachnoid hemorrhage (SAH)
- If SAH → mortality is 50%
- Differentials: Fusiform, dissecting, or mycotic aneurysms

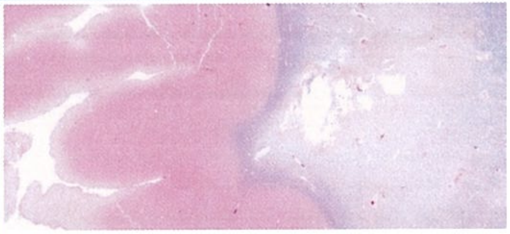
FUSIFORM ANEURYSMS

MORPHOLOGY

- Rare, non-saccular dilation involving the entire vessel wall in short distance
- Often has a periluminal thrombus (jelly consistency)

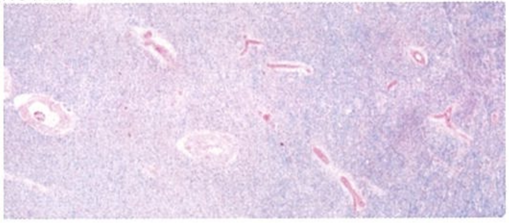
OTHER HIGH YIELD POINTS

- Multiple causes: Atherosclerotic, dissection, disorders of elastin and collagen
- Anterior and posterior circulation
- Treatment via clipping or stenting with coil
- Differential diagnosis includes saccular and mycotic aneurysms

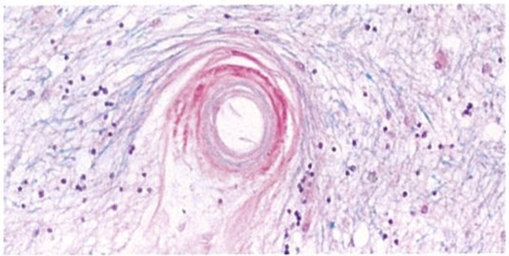


Leukoencephalopathy. Myelin pallor and cavitary infarcts.

CADASIL. PAS showing thick vessel walls in a patient with NOTCH3 mutation



Leukoencephalopathy. Myelin pallor and cavitary infarcts



CADASIL. High-power view of affected blood vessel shows granular PAS positivity

CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL)

MORPHOLOGY

- Rare small vessel arteriopathy
- Progressive ischemic damage
- Cortex is usually uninvolved but may present with atrophy
- PAS-positive granular vascular deposits
- Electron microscopy: Granular osmiophilic material (GOM) in affected vessels

OTHER HIGH YIELD POINTS

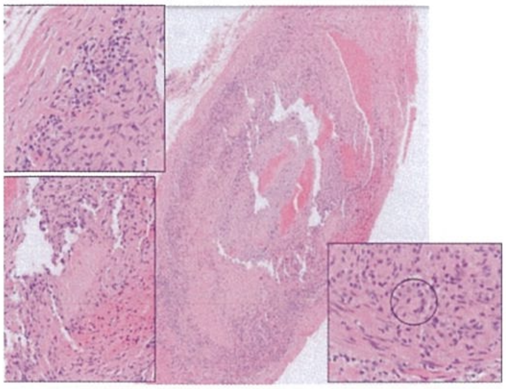
- **NOTCH3 gene mutations**
- Molecular diagnosis: Specific genetic test for NOTCH3 mutation (whole blood)
- Previously called familial Binswanger disease, chronic familial vascular encephalopathy
- Migraine, ischemic attacks (onset at 50th decade)
- Psychiatric disturbances can progress to dementia (80% with dementia at 65 years old); epilepsy is associated with later stage
- Death usually occurs 15-25 years after onset of vascular symptoms
- Skin biopsy can be used for diagnosis (57% sensitive and 100% specific)
- Differential diagnosis: Hypertensive cerebrovascular disease, thromboembolic disease, cerebral amyloid angiopathy

Path Presenter

2. CEREBROVASCULAR DISEASE

VASCULITIS

Temporal artery with giant cell arteritis.



GIANT CELL ARTERITIS

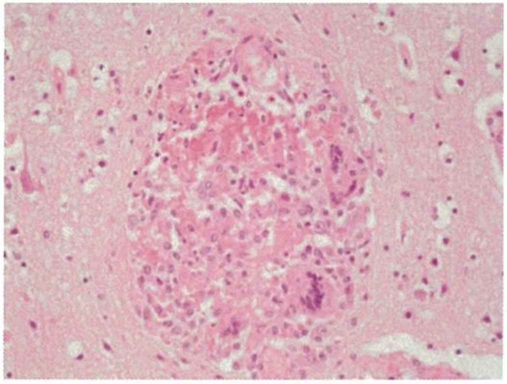
MORPHOLOGY

- Nodular swellings on the affected artery
- Transmural cell infiltrate (lymphocytes, monocytes, macrophages)
- Granulomas, multinucleated giant cells, and T-lymphocytes
- Fragmentation and phagocytosis of the internal elastic lamina
- Intimal proliferation and reduced luminal diameter

OTHER HIGH YIELD POINTS

- Incidence is 15 cases per 100,000 persons
- Peak at 75-85 years old
- Twice as common in females
- Differential diagnosis: Other forms of vasculitis

Primary angiitis of the CNS- granulomatous inflammation affecting small arteries



PRIMARY ANGIITIS OF THE CNS (PACNS)

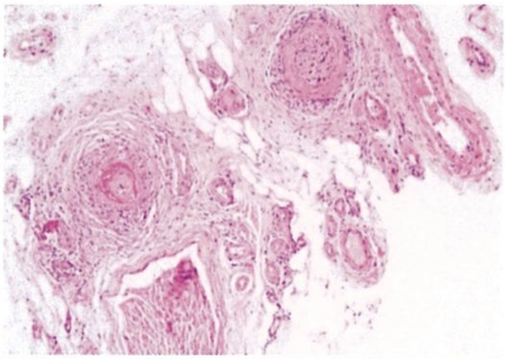
MORPHOLOGY

- Idiopathic vasculitis affecting parenchyma and meningeal arteries
- Intimal granulomatous inflammation, transmural lymphocytic infiltration of small- and medium-sized arteries, multifocal

OTHER HIGH YIELD POINTS

- Rare; 2:1 male predominance
- Headache and stroke-like symptoms
- Poor prognosis, mean survival is 45 days at the time of diagnosis
- Angiography is diagnostic: Beading, luminal narrowing, single or multifocal occlusions, avascular mass effect
- Acid-fast bacilli and fungus stains necessary to rule out infectious etiology
- Congo red stain and Aβ-amyloid immunostain necessary to rule out ABRA
- Differential diagnosis: Sarcoidosis, infectious granulomatous disease, intravascular lymphoma, cerebral amyloid angiopathy with vasculitis (ABRA)

Peripheral nerve with vasculitis



POLYARTERITIS NODOSA

MORPHOLOGY

- Systemic vasculitis that involves medium-sized arteries of any organ (except lungs and spleen)
- Segmental, transmural acute inflammation of the vessel wall with fibrinoid necrosis

OTHER HIGH YIELD POINTS

- Associated with immune complexes
- Peripheral nerves are the most commonly involved part of the nervous system (nerve involvement has strong association with hepatitis B and C)
- Associated diseases: Cryoglobulinemia, Sjögren syndrome, HIV, arthritis
- Differential diagnosis: Sarcoidosis, infectious granulomatous disease, cerebral amyloid angiopathy with vasculitis (ABRA)

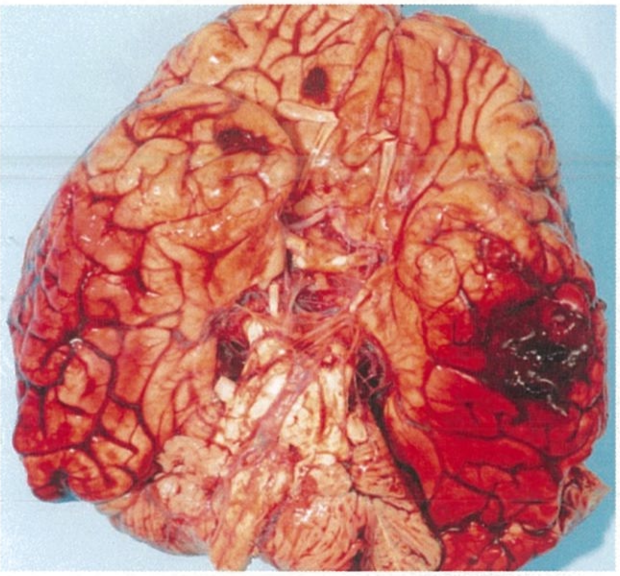
MOYAMOYA DISEASE

MORPHOLOGY

- Progressive stenosis of intracranial carotid arteries and proximal branches with abnormal vessel formation
- Bimodal age distribution; Asian population more likely to be affected when primary
- 2:1 female predominance
- Associated diseases, when secondary: Down syndrome, neurofibromatosis type 1, and sickle cell disease
- If bilateral involvement, anterior and posterior circulation affected → worse prognosis
- Effacement of the media and disruption of the internal elastic lamina

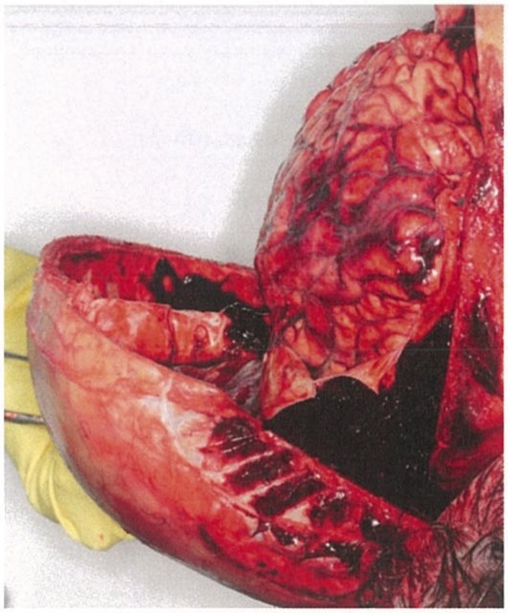
OTHER HIGH YIELD POINTS

- Associated with chromosomes 3p24.2-p26, 17q25, and 8q23
- Differential diagnosis: Post-irradiation arteriopathy, thrombosis, infection



TRAUMA

MICHAEL KRISTELIS, MD
RAQUEL T. YOKODA, MD



Picture courtesy: Gregory Dickinson, MD

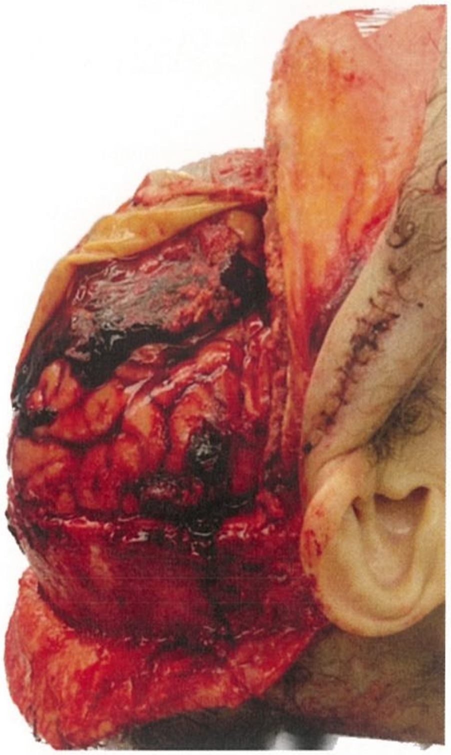
EPIDURAL HEMATOMA (EDH)

MORPHOLOGY

- Ovoid mass composed of blood between the dura and inner table of the skull

OTHER HIGH YIELD POINTS

- Most commonly due to the fracture of the squamous temporal bone causing **laceration of the middle meningeal artery**
- Up to 30% of cases may be associated with a "lucid interval"
  - A period of variable duration after the head injury
  - Without initial clinical manifestations
  - Occurs before the development of an often-rapid decline in neurologic function
- Other sites of involvement include the anterior cranial fossa (anterior meningeal artery), parasagittal region (superior sagittal sinus), and occipital lobe and posterior fossa (occipital meningeal artery or transverse or sigmoid sinuses)
- Posterior cranial fossa EDH may occur in infants and young children from damage of a sinus in the absence of an overlying skull fracture
- Spontaneous EDH has been described in association with vascular malformations, infections, and complications of metastatic disease and anticoagulation therapy



Picture courtesy: Raquel Yokoda, MD

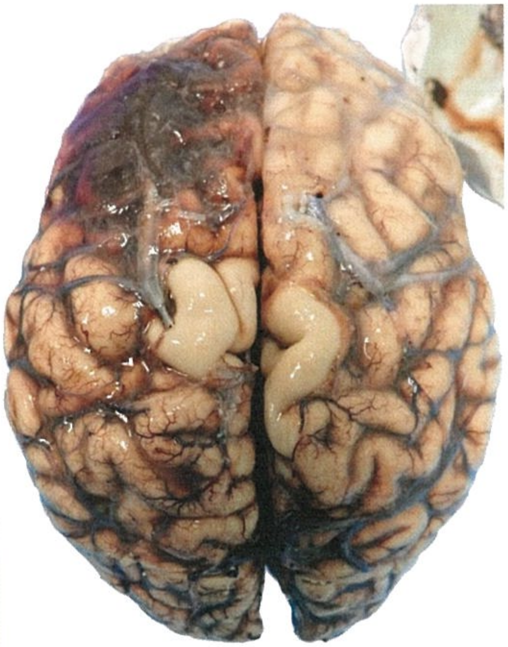
SUBDURAL HEMORRHAGE (SDH)

MORPHOLOGY

- Macroscopic findings
  - Acute: Dura is tense, with underlying fresh blood that spills out during surgery or autopsy
  - Subacute: Blood clot shows at least focal attachment to the dura, with possible golden brown color change due to hemosiderin deposits
  - Chronic: Blood clot encapsulated in fibrous membranes, containing blood products of different ages
- Reactive fibroblasts appear at the dural interface within **3-5 days**, and granulation tissue is evident along the dural surface by **5-10 days**
  - By **3-4 weeks**, the fibrovascular membrane can equal the dural thickness
- If the hematoma is thick, clotted blood persists between the dura and arachnoid for **weeks to months**
  - A thin fibrovascular membrane forms at the arachnoid surface beginning at **10-20 days** and gradually thickens

OTHER HIGH YIELD POINTS

- Classified as acute, subacute, or chronic
  - Acute: Present approximately 6 hours to 3 days following injury
  - Subacute: Present approximately 3 days to 3 weeks following injury
  - Chronic: Present greater than 3 weeks following injury
- Acute SDH typically presents after blunt force head injury
  - Rupture of bridging vein (more common with brain atrophy)
  - Damage to cortical veins or arteries and overlying leptomeninges
  - **Burst lobe:** Intracranial hemorrhage continuous with subdural hemorrhage, seen in **extensive laceration injury**



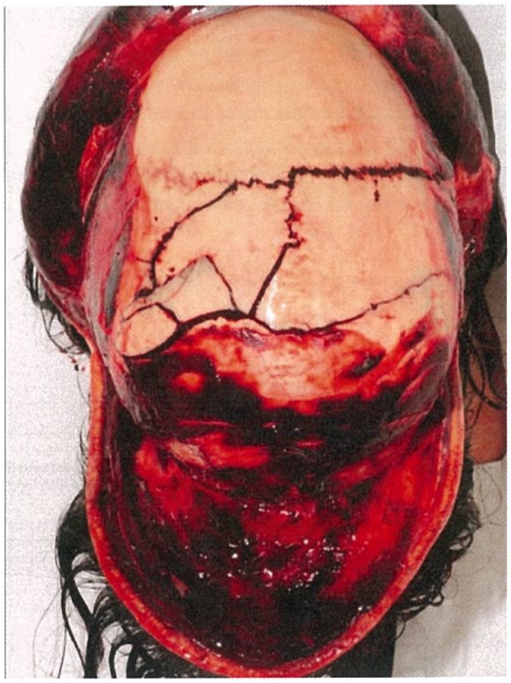
Picture courtesy: Raquel Yokoda, MD

SUBARACHNOID HEMORRHAGE (SAH)

HIGH YIELD POINTS

- Commonly observed and typically associated with damage to leptomeningeal veins in the subarachnoid space or related to sites of contusions
- In itself, not necessarily of clinical or prognostic significance
  - **Exception: Massive basal traumatic subarachnoid hemorrhage**
- Massive basal traumatic subarachnoid hemorrhage
  - Typically seen in the setting of vertebral artery injury
    - Well described following a blow to the inferior aspect of the jaw with associated rotation and hyperextension of the head, which results in tearing of the vertebral artery
  - Clinically presents as sudden collapse and coma, usually with a short survival period
  - Extensive basal hemorrhage can mimic the events associated with a ruptured berry aneurysm
    - Postmortem angiography can help confirm the site of vascular injury
    - Postmortem examination includes careful dissection of the vertebral arteries from the point at which they enter the foramina transversally at the lower cervical vertebrae and enter the base of the skull
    - Site of traumatic rupture is typically where the vertebral artery passes through the dura into the intracranial component

FRACTURES



Picture courtesy: Gregory Dickinson, MD

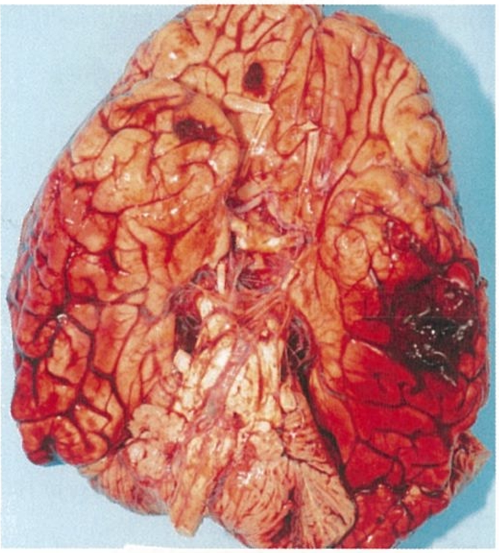
SKULL FRACTURES

MORPHOLOGY AND OTHER HIGH YIELD POINTS

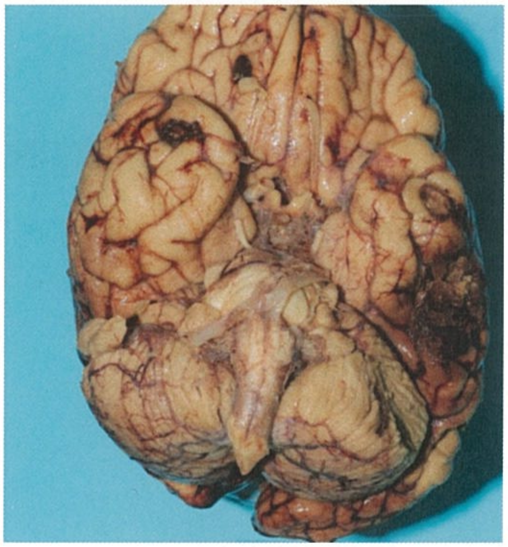
- Classification is based on the location and extent of involvement of the skull as well as surrounding structures
- **Linear:** Both outer and inner tables of the skull are involved with no bone displacement
- **Hinge (basilar):** Linear fracture that extends across the base of the skull
- **Depressed:** Fragments of the inner table of the skull are displaced inward
- **Compound:** Depressed fracture with associated scalp laceration
- **"Ping pong":**
  - Depressed fracture caused by inner buckling of the calvarium
  - Fracture line is not visualized radiographically
  - Not associated with a break in the inner table of the skull
  - Rarely is associated with underlying parenchymal injury
- **Diastatic:** Fracture line extending along skull bone sutures, causing widening of the sutures
- **Growing:** Due to the extension of meninges through a fracture, preventing healing
- Complex or penetrating fractures are associated with additional dural tearing
- No direct correlation can be drawn between the presence or absence of a skull fracture and the likelihood of an underlying parenchymal lesion
  - **Exception: The fracture is depressed, and the broken bone makes direct contact with the underlying brain tissue**
- There does seem to be a correlation between the presence of a skull fracture and the development of intracranial hemorrhages
- One can also see scalp lesions, such as contusions or lacerations, overlying the site of the skull injury

3. TRAUMA

CONTUSIONS



Fresh and fixed brain contusion
Picture courtesy: Gregory Dickinson, MD



Fresh and fixed brain contusion
Picture courtesy: Gregory Dickinson, MD

CONTUSIONS

MORPHOLOGY

- Essentially bruises on the surface of the brain
- Two prototypical patterns: *coup and contrecoup*
  - *Coup* occurs at the site of impact
  - *Contrecoup* occurs at the site opposite of the impact
- Typically involve the frontal poles; the inferior frontal lobe, including the gyrus rectus and medial and lateral orbital gyri; the temporal poles and lateral and inferior aspects of the temporal lobes; and the cortex above and below the Sylvian fissure
- Rarely involve the occipital lobes and cerebellum
- Usually associated with a skull fracture
- Typically involve crests of gyri and are often superficial
- Ordinarily **occur in multiple vascular territories and have a characteristic wedge shape, helping to distinguish from infarcts**
- Often, evidence of associated hemorrhage
- Lesions may extend to involve underlying white matter and develop into a hematoma
- **Burst lobe:** Severe cases with extensive laceration injury with underlying parenchymal hemorrhage associated with subdural hemorrhage (SDH)
- Abnormal pigmentation is seen several weeks following injury
- Microscopy of smallest contusions
  - Collections of minute perivascular hemorrhages in the cortex, often only a few millimeters in diameter
  - No appreciable edema
- Microscopy of larger contusions
  - Areas of tissue destruction
  - Often associated with focal swelling
- Macrophages, foci of gliosis, and associated hemosiderin deposition can be seen over time

OTHER HIGH YIELD POINTS

- **Old contusions can be the site of epileptogenic foci**
  - Post-traumatic epilepsy accounts for approximately 5% of all cases of epilepsy

DIFFUSE AXONAL INJURY

Sampling Protocol for Suspected Diffuse Brain Injury

Cerebral Hemispheres	**Brainstem**	**Cerebellum**
Corpus callosum with adjacent parasagittal cortex and white matter	Midbrain at the level of the decussation of the superior cerebellar peduncles	Cerebellar hemisphere, including the dentate nucleus
Genu (anterior sections of corpus callosum)	Pons at the level of the middle cerebellar peduncles	
Temporal lobe, including hippocampus	Medulla	
Deep gray matter, including posterior limb of internal capsule		

DIFFUSE AXONAL INJURY (DAI)

MORPHOLOGY

- **Traumatic axonal injury (TAI) is the neuropathologic substrate of DAI**
- In moderate to severe cases of TAI, grossly visible hemorrhagic lesions are present
  - **Grade 1:** Only microscopic changes are seen
  - **Grade 2:** Focal hemorrhagic lesions present in the corpus callosum only
  - **Grade 3:** Lesions seen in Grade 2 plus additional focal hemorrhagic lesions present in the dorsolateral quadrants of the rostral brainstem
- **TAI is classified as focal or diffuse based on histopathologic examination**
- Damaged axons can be **seen on H&E as eosinophilic swellings** and highlighted on silver stains
  - Limitation: Silver stains only highlight abnormal axons after a survival period of at least 12-18 hours
- Microglial activation, followed by the formation of microglial "clusters" or "stars" around degenerating axons, are seen in subjects who survive 5-10 days after TAI
- Long-term survival → areas of long tract degeneration → glial scarring

OTHER HIGH YIELD POINTS

- Immunohistochemistry for **beta-amyloid precursor protein (β-APP)** is the most sensitive and widely used method to highlight damaged axons
  - Has been demonstrated in subjects who have survived for a period as short as 35 minutes from the time of injury
  - Limitation: β-APP is a marker of axons with perturbation of axonal flow and, therefore, can accumulate in other conditions such as ischemia
- Distinguishing **TAI from ischemia on β-APP immunohistochemistry**
  - TAI: Linear staining pattern along white matter tracts ("beads on a string")
  - Ischemia: Zig-zag staining pattern within the area of compromised blood supply
- DAI is a clinical diagnosis in patients with immediate, prolonged coma and supportive radiologic findings
- **TAI**
  - Contributes to at least 35% of the mortality and morbidity of TBI cases without associated space-occupying lesions
  - Considered to be a significant cause of severe disability and vegetative state in survivors of head injury
- Areas of particular vulnerability in TBI include white matter bundles such as the corpus callosum, internal capsule, cerebellar peduncles, and descending tracts in the brainstem
- As such, these areas are recommended for sampling in the evaluation for TAI (see table above)

FAT EMBOLI

FAT EMBOLI

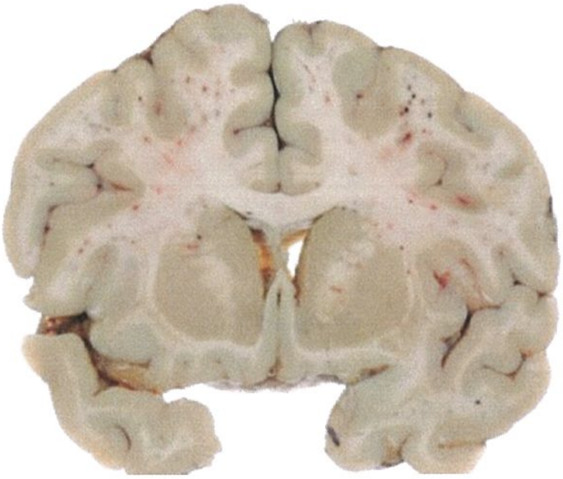
MORPHOLOGY

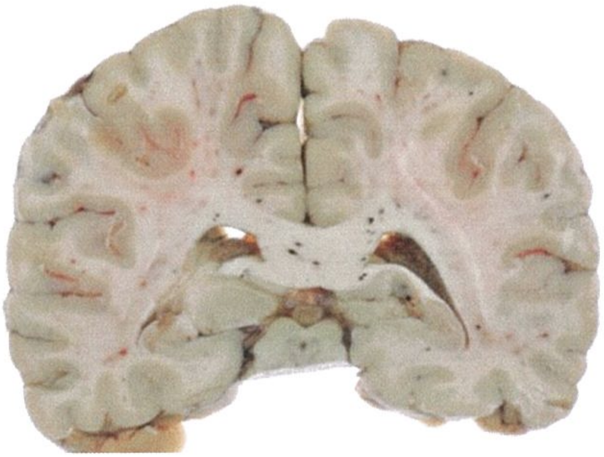
- Diffuse cerebral edema
- Widespread petechial hemorrhages
- Examination of **frozen brain tissue** with histochemical staining for lipids (e.g., oil red O) is performed to assess for the presence of fat emboli
  - White matter appears to sustain injury more frequently

OTHER HIGH YIELD POINTS

- Results from injury to fat-containing tissues (e.g., bone fractures)
- Neurologic and respiratory symptoms usually 12-72 hours after injury

Picture courtesy: Timothy Richardson, DO, PhD





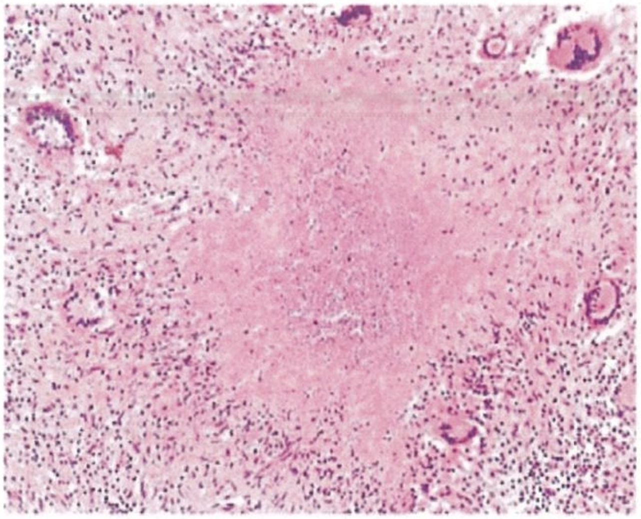
3. TRAUMA

PEDIATRIC HEAD TRAUMA

PEDIATRIC HEAD TRAUMA

HIGH YIELD POINTS

- Non-abusive
  - Perinatal
  - Can result from excessive molding of the cranial bones or excessive force applied to the skull during delivery
  - Asymptomatic perinatal acute SDH is common and associated with compressive forces of uterine contraction during labor
  - Life-threatening acute SDH is traumatic in nature
- Tentorial laceration: Massive infratentorial SDH
- Falx laceration: The tear is usually close to the junction of falx and tentorium
- Bridging vein rupture: Can be bilateral
- Pediatric
  - Head injury in children after the age of 9-12 months reflects adult patterns of brain injury, commonly due to falls or road traffic accidents
  - Fatal low-level (< 3 feet) falls are associated with a skull fracture, usually linear, and EDH or SDH
- Can cause intracranial injury without associated soft-tissue injury or skull fracture
- Infants sustain skull fractures more commonly than toddlers
- Cause of death is due to hemorrhage acting as a space-occupying lesion
- Abusive
  - More common in younger infants (< 9-12 months of age)
  - Higher incidence of global brain ischemia and cervicomedullary axonal injury
  - "Triad" of cerebral edema, retinal hemorrhages, and a thin film of SDH/hematoma (often midline)
  - Diffuse TAI is rare unless there is an obvious associated head impact
  - Focal TAI can be seen in the cervicomedullary region
  - β-APP staining can also be seen in spinal nerve roots, either involving the entire cord or accentuated in the lumbosacral region
- Important to rule out non-traumatic causes of intracerebral hemorrhage (e.g., infections, blood dyscrasias, vascular malformations)



INFECTIONS

MICHAEL KRISTELIS, MD

4. INFECTIONS

BACTERIAL CNS INFECTIONS

LEPTOMENINGITIS

MORPHOLOGY

- Neonates: macroscopic
  - Edematous and congested brain with hemorrhagic infarcts
  - Purulent exudate in subarachnoid space over cerebral convexities and/or the base of the brain
  - Ventricles may be compressed or dilated
  - Coexistent cerebral abscesses (*Citrobacter diversus, Proteus mirabilis*)
  - Complications include obstructive or communicating hydrocephalus
- Neonates: microscopic
  - Meningeal exudate containing large numbers of neutrophils, scattered macrophages, fibrin, and necrotic cellular debris
  - Bacteria are usually demonstrable within the exudate
  - Leptomeningeal and cortical arteries and veins can show intimal accumulations and infiltration by inflammatory cells
  - Venous thrombosis and infarction are often evident and may be extensive
- Children and adults: macroscopic
  - Swollen and congested brain
  - Venous thrombosis and hemorrhagic infarcts are less common than neonates
  - Small infarcts may result from thrombosis of penetrating arteries
  - Purulent exudate in the subarachnoid space over the cerebral convexities and the base of the brain
  - There may be little or no discernible exudate in patients dying very acutely or having been partially treated with antibiotics
  - Ventricles may be compressed or dilated, with purulent exudate
  - Ventricular shunt infection leads to pronounced ventricular exudate with clear leptomeninges (ventriculitis)
  - Ventricular hemorrhage may be present due to coagulopathy
  - Complications include cerebral edema, obstructive or communicating hydrocephalus, subdural effusions, or subdural empyema
  - Subdural effusions can result in occasional complications of meningitis in children, accumulations of clear fluid over the cerebral convexities or in the interhemispheric fissure
- Children and adults: microscopic
  - The first few days show large numbers of neutrophils and necrotic debris comprising the subarachnoid and ventricular exudate
  - Intracellular and extracellular bacteria can usually be demonstrated
  - Extends along perivascular spaces, and purulent material is usually present in the choroid plexus
  - Lymphocytes and macrophages increase in number with time, predominating by the end of the first week
  - Leptomeningeal and cortical blood vessels can show intimal accumulations and infiltration by inflammatory cells
  - Fibroblastic proliferation and thrombosis with associated focal infarction are common
  - Hemorrhagic meningitis is often seen in infection with *Bacillus anthracis*

OTHER HIGH-YIELD POINTS

- Neonates
  - Group B streptococci and *Escherichia coli* account for over 65% of cases of neonatal bacterial meningitis in developed countries
  - The initial portal of entry is usually oral, with hematogenous spread to the CNS
  - Initial symptoms are non-specific (e.g., poor feeding, diarrhea, vomiting, irritability)
  - The mortality rate is 30-60%
  - Long-term morbidity (e.g., mental retardation, epilepsy, hydrocephalus, spasticity, deafness, and blindness) affects approximately 35% of survivors
- Children and adults
  - **Children** (especially aged between 1 month and five years): *Hemophilus influenza* type b and *Neisseria meningitides* (meningococcus) are responsible for approximately 80% of cases, and *Streptococcus pneumoniae* accounts for a further 10-20% of cases
  - **Adults**: *Streptococcus pneumoniae* accounts for up to 50% of all cases; *Neisseria meningitides* is slightly less common overall; infection tends to occur in outbreaks and is facilitated by crowded living conditions and poor hygiene (e.g., college dorms, military barracks)
  - Gram-negative bacilli are responsible for approximately 65% of cases of meningitis complicating neurosurgery, and a smaller but significant portion occurs after head injury
  - Ventriculitis and meningitis caused by slime-producing strains of *Staphylococcus epidermidis* are seen in patients with ventricular or lumbar shunts
  - *Bacillus anthracis*: industrial, bioweapons- or bioterrorism-related meningitis

- **Typically presents with pyrexia, headache, vomiting, nuchal rigidity, and photophobia;** seizures, cranial nerve palsies, or focal neurologic deficits may also develop
- Mortality varies between about 5-40%; it depends on age, the responsible agent, and the presence of specific risk factors

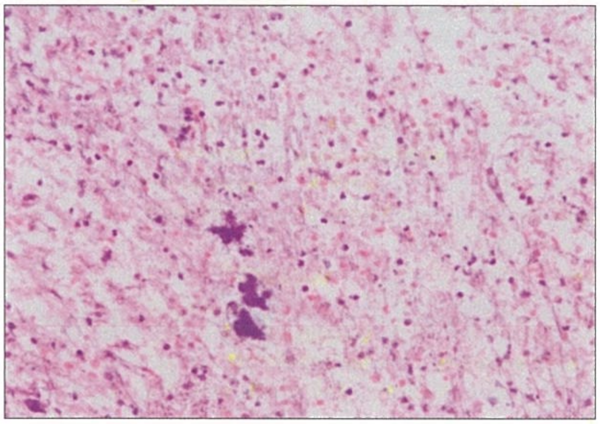
ABSCESSES

MORPHOLOGY

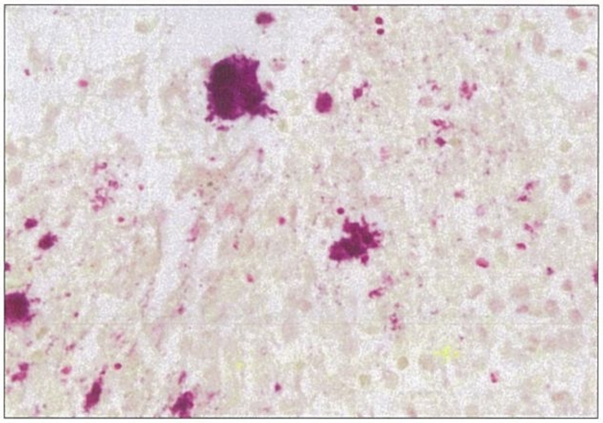
- Macroscopic:
  - Visible capsule with a purulent central region
  - Capsule gradually thickens over time; greater extent seen in the subcortical region (relatively thin in the deep white matter)
  - 1-3 weeks to become macroscopically discernible (preceded by ill-defined region of hyperemia with surrounding white matter edema; cerebritis)
  - Single abscesses in the frontal lobes, temporal lobes, or anterior parietal region can be seen in **direct extension of local infection**
  - Cerebellar abscesses may occur as a **complication of otogenic infection**
  - *Listeria monocytogenes* has a predilection for the brainstem resulting in purulent rhombencephalitis
  - Multiple abscesses involving the gray/white matter junction tend to be seen in **hematogenous spread of infection** (in the perfusion territory of the middle cerebral arteries mostly)
  - Epidural abscesses can be seen in the spinal canal (mostly) or intracranially
- Microscopic:
- Focal suppurative encephalitis (day 1-2)
  - Swelling of endothelial cells, perivascular and parenchymal infiltration by neutrophils, occasional mononuclear inflammatory cells, and rapidly developing small foci of necrosis
  - Focal suppurative encephalitis with confluent central necrosis (day 2-7)
  - Foci of necrosis becoming increasingly large and confluent, more numerous foamy macrophages present (by day 3 or 4), as well as lymphocytes and plasma cells now present within the inflammatory infiltrate
- Early encapsulation (day 5-14)
  - Granulation tissue response with newly formed capillaries and scattered fibroblasts, which then proliferate and deposit reticulin, present around the margin of necrotic tissue
  - Bacterial brain abscesses associated with septicemia in immunocompromised patients may show extensive necrosis with little or no encapsulation
  - Surrounding brain tissue is edematous and contains swollen reactive astrocytes
  - Parenchymal blood vessels have plump endothelial cells and tend to be surrounded by small aggregates of lymphocytes
- Late encapsulation (from day 14)
  - Capsule is now composed of multiple concentric layers of fibroblasts and collagen, with variable numbers of inflammatory cells, mainly lymphocytes and macrophages
  - Thickness of the capsule increases over subsequent weeks due to progressive collagen deposition
  - Capsule tends to be thicker on the cortical aspect compared to the ventricular aspect
  - Central necrotic material with a surrounding rim of granulation tissue and reactive brain tissue may still be present
  - Granulation tissue contains numerous neutrophils, foamy macrophages, and scattered lymphocytes
- Occasionally, the infection will resolve in the absence of treatment, leaving behind the dense fibrous capsule lined by sparse macrophages and amorphous material

OTHER HIGH-YIELD POINTS

- Caused by direct spread of local infection or hematogenous spread
- Direct spread accounts for approximately 50% of brain abscesses; tends to occur in the frontal lobes, temporal lobes, or the anterior parietal region
- Hematogenous spread accounts for approximately 25% of brain abscesses
  - Children: **congenital heart disease with right-to-left shunting** (bypassing of pulmonary circulation by small septic emboli cerebral hypoxia, and increased blood viscosity due to polycythemia are probably all contributory factors)
  - Adults: **septic emboli**
- Headache, fever, epilepsy, nausea and vomiting, altered sensorium, nuchal rigidity, or localizing neurologic signs may be observed
- Mortality approximately 20%
- Persistent epilepsy, intellectual impairment, focal neurologic signs, or a combination of these are seen in approximately 50% of survivors



H&E stain demonstrating necrosis, inflammation and clusters of bacterial organisms
Picture courtesy: Dr. Steven Schwartz



Gram stain showing Gram-positive cocci

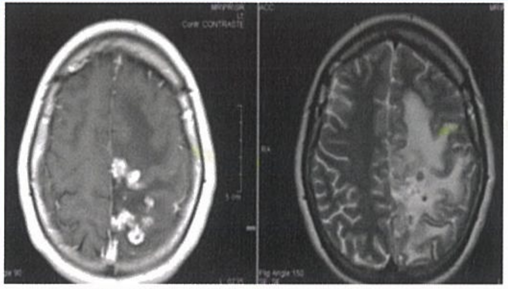
SEPTIC EMBOLISM

MORPHOLOGY

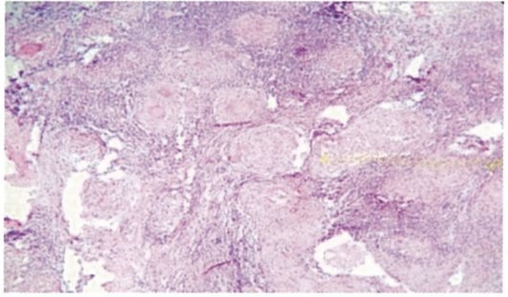
- Composed of an admixture of fibrinous material, red blood cells, and inflammatory cells
- Interspersed bacterial organisms may be seen on routine histology and/or with Gram stain

OTHER HIGH-YIELD POINTS

- Source of hematogenous spread of infection
  - Adults: bronchiectasis, lung abscess, subacute endocarditis; *Streptococcus viridans,* microaerophilic and anaerobic streptococci (*Listeria monocytogenes* in older people)
  - Children: congenital heart disease with right-to-left shunting; *Listeria monocytogenes* in neonates



MRI imaging demonstrating multiple tuberculosis lesions
Picture courtesy: Dr. Louis Carius



Multiple granulomas seen in a case of tuberculosis

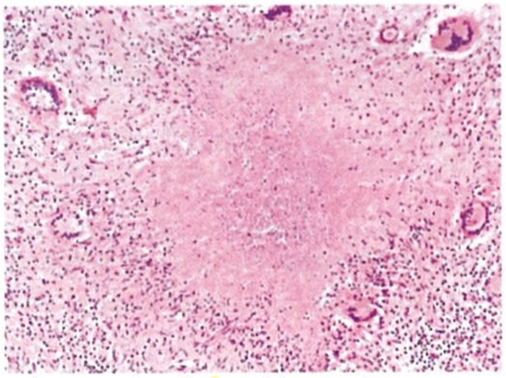
MYCOBACTERIUM TUBERCULOSIS

MORPHOLOGY

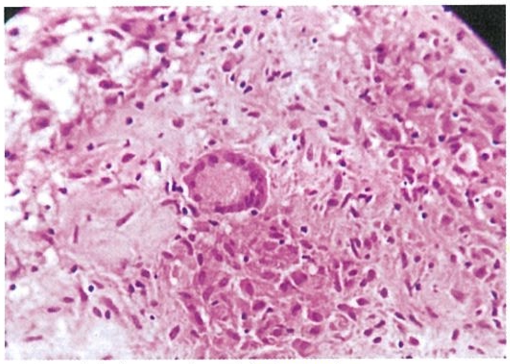
- Can involve the leptomeninges (tuberculous meningitis) as well as the CNS parenchyma (tubercles/ tuberculomas)
- Can also affect the spinal canal through the extension of tuberculous vertebral osteomyelitis into the epidural space

Macroscopic:

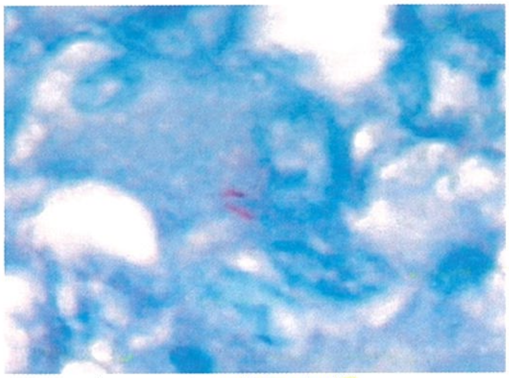
- **Tuberculous meningitis**: gelatinous subarachnoid exudate
  - Usually thickest in the Sylvian fissures, over the base of the brain, and around the spinal cord
  - Usually also present within the choroid plexus and lining the ventricles
- **Tubercles/ Tuberculomas:** encapsulated yellow or gray masses
  - Can be solitary or multinodular aggregates of smaller masses
  - Central tissue is necrotic, with a firm consistency
  - Most often cerebral or cerebellar, but can occur anywhere within the neuraxis
  - Tubercles within the leptomeninges and ventricular lining, as well as small superficial cortical tuberculomas are common in patients with meningitis
  - Rich's focus: persisting primary tubercle within the CNS; reactivation and rupture into the subarachnoid space or ventricles results in tuberculous meningitis
- Moderate ventricular dilatation due to obstructive or communicating hydrocephalus can be seen in patients with tuberculous meningitis
- Infarcts can be seen in tuberculous meningitis due to arteritis
- Common in the superficial cortex and basal ganglia, the latter due to involvement of perforating branches of the middle meningeal artery



Higher power view of a necrotizing granuloma



Histiocytic inflammation with giant cells



AFB stain demonstrating acid-fast bacilli

Picture courtesy: Dr. Silvia J. Hernandez

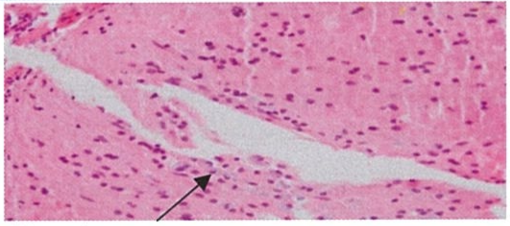
- Involvement of the spinal column usually shows extensive destruction with collapse of affected vertebral bodies and intervertebral discs, as well as variable protrusion of gray multinodular granulomatous tissue into the epidural space

Microscopic:

- **Meningitis:** exudate contains lymphocytes, macrophages, and sparse plasma cells, admixed with necrotic material and fibrin
  - ➢ Inflammation extends into the subpial and periventricular brain parenchyma and can involve the walls of blood vessels within the exudate to varying degrees
  - ➢ Thrombosis and subintimal/ intimal fibroblastic reaction can cause occlusion of the vascular lumen, resulting in infarcts
- **Tubercles/ Tuberculomas**: central caseous necrosis surrounded by lymphocytes, epithelioid cells, and Langhans-type multinucleated giant cells, with an outer zone of collagen, fibroblasts, lymphocytes, and macrophages
  - ➢ Special staining for reticulin reveals loss within the caseous material, useful for distinguishing from gummas
  - ➢ Older lesions may calcify
  - ➢ Less granulomatous inflammation with a lack of multinucleated giant cells seen in immunosuppressed patients
  - ➢ Mycobacteria may be readily demonstrable or very sparse; highlighted by special staining for acid-fast organisms (e.g., Kinyoun)
- Adjacent brain parenchyma to both meningitis and tubercles/ tuberculomas can be markedly gliotic
- Epidural nodules in spinal canal involvement will show the same granulomatous inflammation with caseation
- Spinal cord shows a combination of focal compression by the epidural inflammatory tissue or vertebral kyphosis, ischemia, and secondary long tract degeneration

OTHER HIGH YIELD POINTS

- *Mycobacterium tuberculosis* is the usual causative agent
- *Mycobacterium bovis* rarely causes meningitis
- *Mycobacterium avium-intracellulare* (MAC): immunosuppressed patients
- Vaccination with attenuated Bacille Calmette-Guérin (BCG) strain occasionally produces disseminated disease, including meningitis, in immunosuppressed patients



Macrophages

WHIPPLE'S DISEASE

MORPHOLOGY

Macroscopic:

- Foci of granular yellow or gray discoloration involving
  - ➢ Thalamus
  - ➢ Hypothalamus
  - ➢ Cerebellar dentate nuclei
  - ➢ Periaqueductal parenchyma

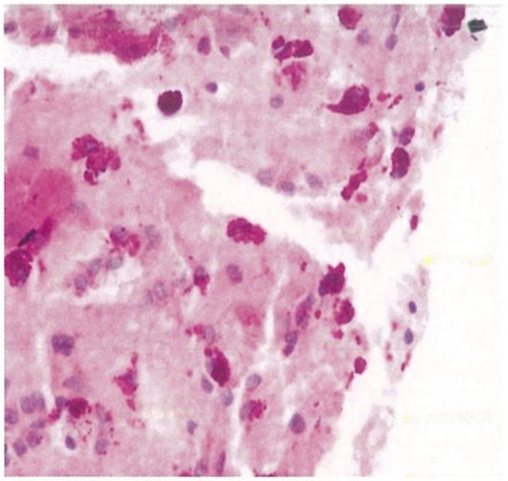
Microscopic:

- Meningeal and parenchymal clusters of macrophages
- PAS-positive, diastase-resistant material within Gram-positive intracellular bacilli, may be difficult to demonstrate due to degenerative changes
  - ➢ Methenamine silver stain demonstrates them reasonably well

  - EM demonstrates them as well as accumulations of membranous material
- Scanty lymphocytic infiltrate
- Thickening and fibrosis of arterial and arteriolar walls in affected areas
- May lead to small infarcts

OTHER HIGH YIELD POINTS

- The causative organism is *Tropheryma whipplei*
- Usually involves intestines (malabsorption, weight loss, diarrhea)
  - CNS involvement results in ophthalmoplegia, oculomasticatory myorhythmia, facial or ocular myoclonus, sleep disturbances, confusion, dementia and raised ICP
- Specific bacterial 16S rRNA sequences can be readily detected in infected tissue and CSF by PCR



PAS stain showing collections of *Tropheryma whipplei* organisms within macrophages

Picture courtesy: Dr. Steven Schwartz

NEUROSYPHILIS

MORPHOLOGY

Macroscopic:

- Leptomeninges thickened and fibrotic
- Underlying brain firm and atrophic
- Cut sections may reveal infarcts (secondary to arteritis, see below) and hydrocephalus
- Gummas appear similar to tubercles/tuberculomas
  - Rare, but can be seen in the leptomeninges and the parenchyma as space-occupying lesions

Microscopic:

- Inflammatory infiltrate containing lymphocytes and plasma cells
  - Can involve leptomeninges, blood vessels, cranial nerves, brain parenchyma, and dorsal root ganglia
  - Degree of inflammation is often mild, with scattered to scant inflammatory infiltrate seen
- The cerebral cortex also shows moderate neuronal loss, reactive gliosis, and marked microglial proliferation
- Spirochetes demonstrable by a silver stain in a minority of cases
- Periventricular white matter may show gliosis
- Arteritis involves arteries of all caliber and arterioles
  - Infiltrates adventitia and media
  - Intima demonstrates concentric collagenous thickening with eventual occlusion and resulting infarction of the surrounding brain or spinal parenchyma
- Spinal cord shows moderate to marked loss of neurons in dorsal root ganglia, with associated satellite cell proliferation (nodules of Nageotte), depletion of dorsal root fibers, and posterior column degeneration
  - Most marked in the lumbar region

OTHER HIGH YIELD POINTS

- Characteristic of tertiary syphilis
- Clinical symptoms associated with regions affected
- **Syphilitic meningitis**: 1-2 years after initial infection
  - Typical clinical manifestations of meningitis plus cranial nerve palsies and acute hydrocephalus
- **Meningovascular syphilis**: approximately 7 years after initial infection
  - Headache, apathy, irritability, insomnia, and focal neurological deficits (based on the distribution of arteritis)
- **General paresis**: 10-20 years after initial infection
  - More common in men
  - Insidious impairment of attention and cognition, followed by psychiatric disturbances, progressive intellectual decline, seizures, loss of motor control, incontinence, and eventual death in the absence of treatment
- **Tabes dorsalis**: 15-20 years after initial infection
  - 'Lightning pains', paresthesia, or both, in the distribution of the involved nerve roots is initially seen, followed by loss of pain and proprioceptive sensation (Charcot's joints, ulceration of feet, shuffling broad-based gait)
- **Congenital neurosyphilis**: can spread across the placenta from approximately 16 weeks gestation
  - Develops over the first decade of life; produces many of the changes of meningovascular and paretic neurosyphilis

LYME DISEASE

MORPHOLOGY

- No macroscopic abnormalities

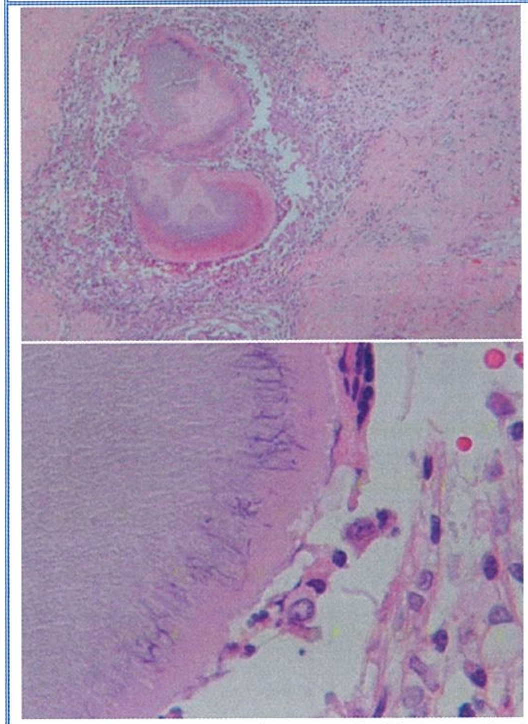
Microscopic:

- **Peripheral nerve biopsy findings** are
  - Perivascular inflammation
  - Axonal degeneration (chronic)
- **CNS findings** are varied (case reports)

  - Chronic meningitis
  - Lymphoplasmacytic parenchymal brain infiltrates
  - Microglial nodules
  - Astrocytosis
  - Neuronal loss with spongiform change
- Spirochetes are demonstrable by silver impregnation (Warthin-Starry or modified Dieterle method), immunohistochemistry, or PCR

OTHER HIGH YIELD POINTS

- Caused by *Borrelia burgdorferi*
- Principal vectors are ***Ixodes* ticks**
- Multisystem disorder involving the skin (erythema migrans), cardiovascular system, joints, and peripheral and central nervous systems



Cluster of actinomyces with grains of sulfur in standard stain, surrounded by inflammatory cells

ACTINOMYCES

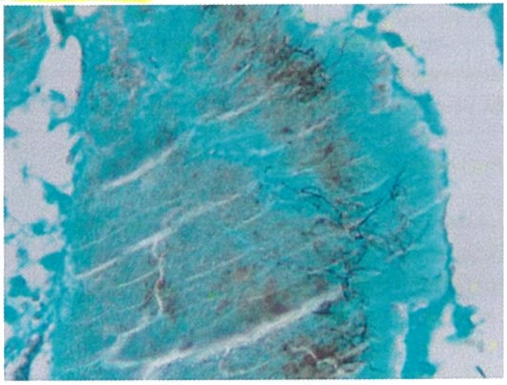
MORPHOLOGY

- Macroscopic:
  - Can present with pachymeningitis and/or intracerebral abscesses
- Microscopic:
  - Characteristic 'sulfur' granules composed of numerous filamentous gram-positive bacteria
  - Strongly labeled with methenamine silver or PAS stains

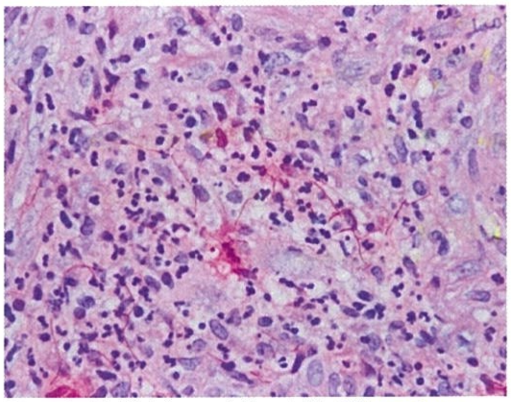
OTHER HIGH YIELD POINTS

- The causative organism is *Actinomyces israelii*
  - Endogenous flora of mucous membranes

Involvement of CNS is rare



Expression of Grocott positive staining in the sulfur granules.
Picture Courtesy: Dr. Martha Tena-Suck



Fite stain highlighting variably acid-fast filamentous organisms
Picture courtesy: Dr. Steven Schwartz

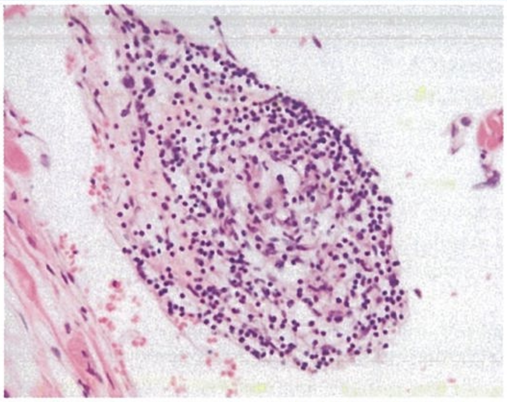
NOCARDIA

MORPHOLOGY

- Macroscopic:
  - Presents as a brain abscess
- Microscopic:
  - Filamentous gram-positive, weakly acid-fast bacteria
  - Can use Gram stain, methenamine silver, or Fite stain
  - Will show a 'beaded' appearance on Fite stain

OTHER HIGH YIELD POINTS

- Causative organisms from the *Nocardia* genus
- More common in immunocompromised patients (>50% of cases)
  - Corticosteroid use is particularly a significant risk factor



Sarcoidosis case showing non-necrotizing granuloma formation.
Picture courtesy: Dr. Steven Schwartz

SARCOIDOSIS

MORPHOLOGY

- Macroscopic:
    - Yellowish-gray thickening of leptomeninges
    - Base of brain is a common location
    - Gelatinous gray material in walls of ventricles and choroid plexus
    - Obstructive hydrocephalus
- Microscopic:
    - Granulomatous inflammation involving meninges, ventricles, choroid plexus, and adjacent brain/spinal cord parenchyma
    - Granulomas are classically non-caseating; may show central fibrosis; necrosis rare
    - Small veins and arteries may be incorporated
    - Rare fibrinoid necrosis and even thrombosis

OTHER HIGH YIELD POINTS

- Inflammatory disorder of unknown etiology
    - Diagnosis of exclusion
- The nervous system is involved in approximately 5% of patients
    - Commonly associated with involvement of PNS and muscle
    - The most common clinical manifestation is facial nerve palsy
    - Other symptoms include deafness, vertigo, aseptic meningitis, hydrocephalus, diabetes insipidus, or hypopituitarism
    - Rare: optic atrophy, ataxia, hemiparesis, and epilepsy

CHRONIC PACHYMENINGITIS

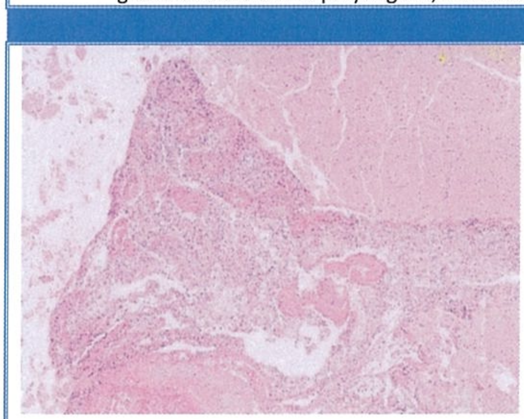
MORPHOLOGY

- Macroscopic:
    - Thickened dura with a slightly nodular appearance
- Microscopic:
    - Collagenous thickening
    - Patchy infiltrations of polymorphic inflammatory infiltrate including lymphocytes, plasma cells, macrophages, multinucleated giant cells and eosinophils
    - Granulomas and necrosis have been reported

OTHER HIGH YIELD POINTS

- Symptoms depend on the distribution of the disease
    - Cranial: headache, cranial nerve palsies, ataxia
    - Spinal: radicular pain, weakness, sensory impairment, spasticity, incontinence
    - Diagnosis of exclusion, need to rule out tuberculosis, syphilis, fungal infections, neoplastic processes (e.g., lymphoma), granulomatosis with polyangiitis, rheumatoid arthritis, and other systemic connective tissue/autoimmune disorders

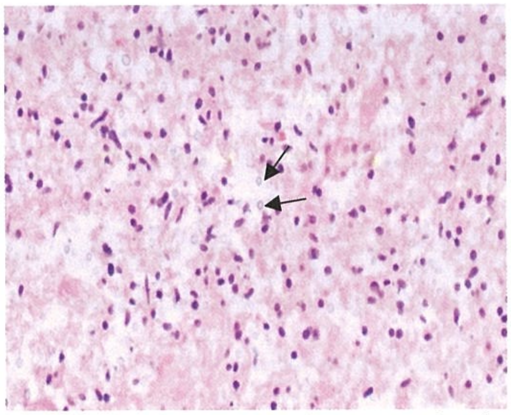
FUNGAL CNS INFECTIONS

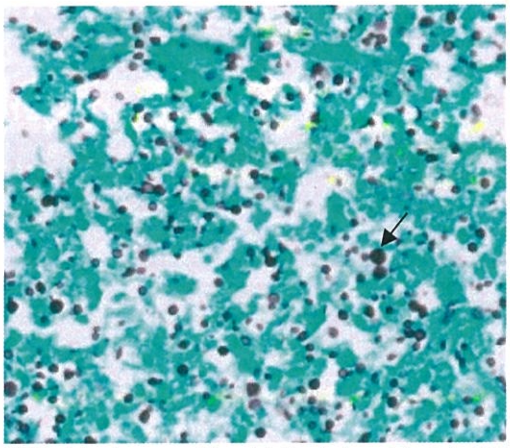


CRYPTOCOCCUS

MORPHOLOGY

- Macroscopic:
- Cryptococcal meningitis
    - Moderately thickened and opacified meninges
    - Slimy consistency is seen in florid infection
    - Small granulomas are rarely seen
    - Yellow-gray exudate in leptomeninges, ventricles, and perivascular spaces seen in some patients with AIDS
    - Leptomeningeal fibrosis seen in subacute or chronic cases
    - Often associated with hydrocephalus
    - Multiple intraparenchymal cysts ('soap bubbles') are also seen in approximately 50% of cases
    - Often prominent in basal ganglia
    - Dura mater is occasionally involved, particularly spinal canal
- Cryptococcal abscesses (cryptococcomas)
    - Variable appearance


Lymphocytic inflammation with intermixed pale-appearing fungal forms (arrows) on H&E stain


GMS stain shows positive staining in fungal forms; note the budding yeasts (arrow) and varying size of fungal forms typical of cryptococcus
Picture courtesy: Dr. Raquel Yokoda

  - Solid gelatinous
  - Granulomatous
  - Resemble bacterial abscesses
  - Occur in the leptomeninges, parenchyma, adjacent to ependymal surfaces, or in the choroid plexus
- Microscopic:
  - Spherical single budding encapsulated yeast
  - Visible on H&E, best seen on PAS staining or methenamine silver stain
  - 'Halo' around stained organisms may be seen due to shrinkage of the capsule during paraffin embedding → can appear similar to corpora amylacea
  - Capsule stains strongly with Alcian blue or mucicarmine
  - Leptomeningeal inflammation composed of collections of lymphocytes, plasma cells, eosinophils, and multinucleated giant cells
  - Cryptococci often visible within the cytoplasm of multinucleated giant cells
  - Granulomas found rarely
  - Cryptococci seen with multinucleated giant cells
  - Gelatinous parenchymal lesions consist of colonies of cryptococci filling and expanding perivascular spaces
  - Cryptococcomas have a variable appearance in terms of density of organisms and inflammatory response

OTHER HIGH YIELD POINTS

- Causative organism: *Cryptococcus neoformans*
- Predisposing factors: AIDS, steroids, hematological malignancy, transplantation, solid tumors
- Low-grade fever, debility, headache, irritability, insomnia, and mild cognitive impairment in patients with meningitis
  - **Most common cause of fungal meningitis**
- Nonspecific features of chronic infection and raised intracranial pressure in patients with cryptococcomas
  - Occasionally asymptomatic and found incidentally at necropsy
- Readily identifiable in preparations of CSF mixed within **India ink**
  - Confirmed by CSF culture or cryptococcal antigen assay

CANDIDIASIS

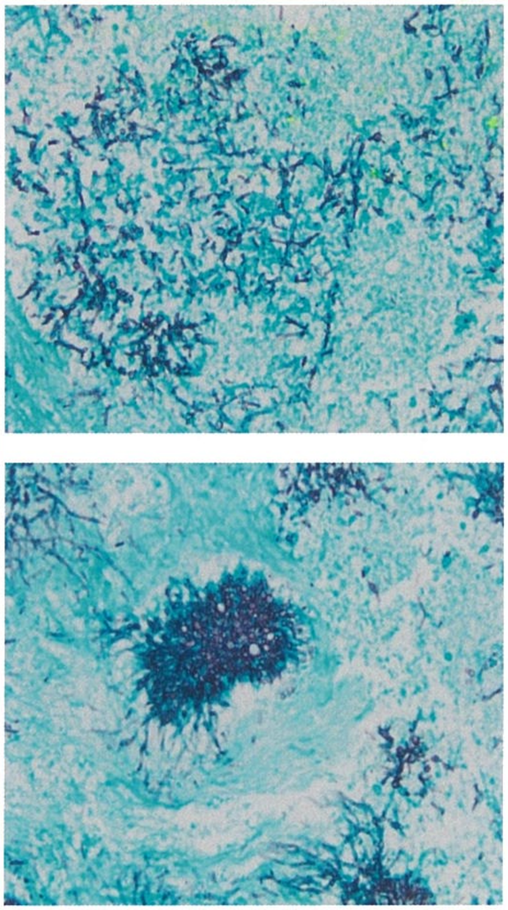
MORPHOLOGY

- Macroscopic:
  - Some cases show no macroscopic abnormalities
  - Scattered hemorrhagic infarcts, most often in the anterior and middle cerebral artery vascular distributions
  - Infarcts evolve into small abscesses or granulomas
- Microscopic:
  - Budding round or oval yeasts
  - Coherence of yeasts after budding forms pseudohyphae
  - True hyphae can be seen with *Candida albicans*
  - Visible on H&E and stain intensely with PAS; well visualized on methenamine silver stain
  - Demonstrable in and around blood vessels and adjacent to foci of necrosis
  - Thrombosed blood vessels with adjacent hemorrhage and infarction
  - Scant lymphocytic infiltration of the meninges
  - Parenchymal inflammatory response is variable
  - Can show no reaction
  - Microabscesses with accumulation of mononuclear and polymorphonuclear leukocytes
  - Small granulomas associated with lymphocytes, macrophages, plasma cells, and occasional multinucleated giant cells

OTHER HIGH YIELD POINTS

- Causative organism: *Candida* species
- Normal intestinal and skin commensals

- Most common mycotic infection of the CNS
    - CNS infection is usually associated with oral thrush and acute or subacute lesions in the vagina, skin, nails, and lungs
    - Relatively late manifestation of systemic candidiasis; cardiac and renal lesions are also usually present
- Symptoms and signs vary with disease involvement
    - Low-grade meningitis: pyrexia, headache, vomiting, nuchal rigidity, and photophobia
    - Diffuse encephalopathy: drowsiness and confusion
    - Abscess: focal neurological deficits
- Predisposing factors: transplantation, burns, antibiotics, trauma, intravenous/urinary catheter, hematological malignancy, solid tumors, steroids, AIDS



Grocott methenamine silver stains highlighting septate fungal hyphae; note the acute angle branching
Picture courtesy: Dr. Steven Schwartz

ASPERGILLOSIS

MORPHOLOGY

- Macroscopic:
    - Single lesions common in direct extension
    - Relatively localized infection, often with fibrosis and granuloma formation
    - Multiple lesions common in hematogenous spread
    - Often occur in anterior and middle cerebral artery vascular distributions
    - Early lesions resemble hemorrhagic infarcts
    - Later on may form abscesses
    - Foci of non-suppurative white or yellow necrotic material admixed with a variable amount of hemorrhagic tissue
    - Granulomas and meningitis are much less frequent
- Microscopic:
    - Infiltration of blood vessels by fungal hyphae
    - Branching at acute angles with regular, septate hyphae
    - Visible on H&E, best seen on methenamine silver stain
    - Morphologically similar to other molds
    - **'Invasive septate hyphae consistent with aspergillosis' is the most accurate diagnosis that can be given on histopathology alone**!
    - Vascular thrombosis, hemorrhage, and infarction
    - Infiltration of vessel walls by fungal hyphae associated with vasculitis, vascular necrosis, and thrombosis
    - Variable inflammatory infiltrate, neutrophils predominate early and macrophages at later stages
    - Chronic lesions can become densely fibrotic with variable inflammation present

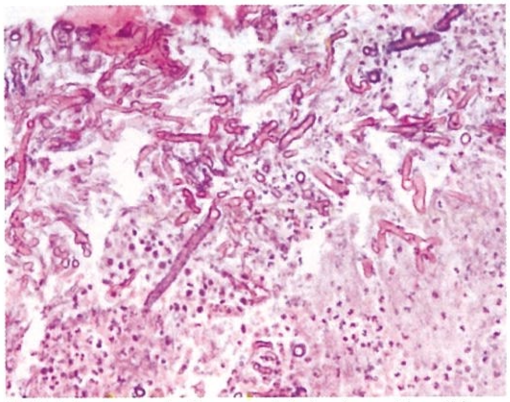
OTHER HIGH YIELD POINTS

- Causative organisms: *Aspergillus* species
- Main predisposing factors: hematological malignancy, diabetes, transplantation
- Headaches, hemiparesis, other focal neurologic deficits, seizures, cranial nerve palsies, and signs of increased intracranial pressure

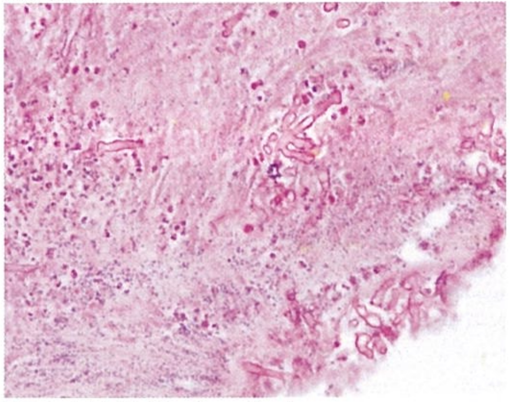
MUCORMYCOSIS/ ZYGOMYCOSIS

MORPHOLOGY

- Macroscopic:
    - Rhinocerebral spread
    - Foci of hemorrhagic necrosis most prominent in the orbital part of the frontal lobes
    - Thrombosis in the cavernous sinus or carotid artery may be seen
    - Hematogenous spread and lesions tend to be concentrated in the basal ganglia
- Microscopic:
    - **Branching at right angles, irregular, non-septate hyphae: DIAGNOSTIC**
    - Visible on H&E, best demonstrated by methenamine silver stain
    - In and around walls of blood vessels in the meninges and brain
    - Admixed hyphae and thrombus occlude the lumina and are associated with extensive hemorrhage



H&E stain demonstrating aseptate hyphae with a ribbon-like appearance



PAS stain highlighting fungal hyphae
Picture courtesy: Dr. Steven Schwartz

  - Mixed or predominantly neutrophil inflammatory response around infiltrated blood vessels and adjacent brain tissue

OTHER HIGH YIELD POINTS

- Causative organisms are the *Zygomycetes* (*Rhizopus, Mucor, Absidia*)
- Main predisposing factors: diabetes, acidosis, dehydration, AIDS, malignancy, transplantation, intravenous drug abuse
- **Rhinocerebral form** usually starts with nasal or unilateral facial swelling and hyperemia
  - **Most common form of mucormycosis**
  - Poorly controlled diabetes and associated episodes of ketoacidosis
- Extension into the orbit produces unilateral ophthalmoplegia, proptosis, edema of the lids, corneal edema, and blindness
- Meningeal infiltration results in severe headaches and nuchal rigidity
- Cerebral blood vessel infiltration results in seizures, aphasia, hemiplegia, lethargy, disorientation, and coma
- Acute fulminant course, leading to death within a few days

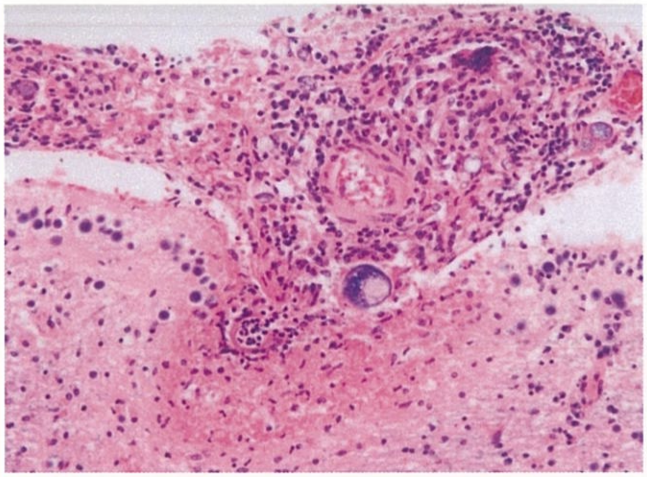
HISTOPLASMOSIS

MORPHOLOGY

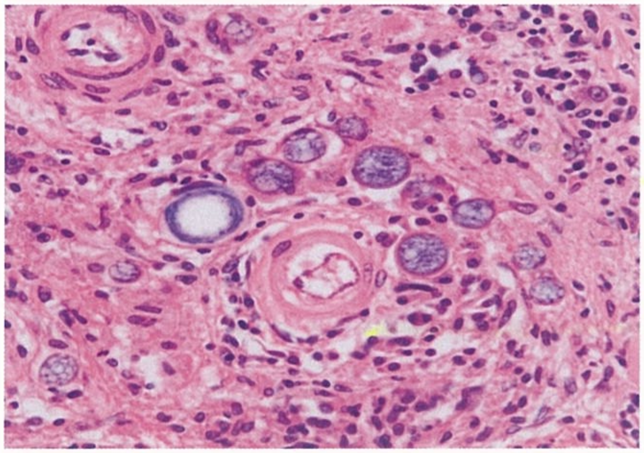
- Macroscopic:
  - Thickened leptomeninges with yellowish-gray exudate (Basal leptomeninges in particular)
  - Miliary granulomas
  - Ependyma and choroid plexus are often involved
  - Small foci of necrosis
  - Infarction of basal ganglia may be seen
- Microscopic:
  - Yeasts visible on H&E, best seen on PAS or methenamine silver stain
  - Intraparenchymal lesions demonstrate **granulomatous inflammation, with yeasts usually found aggregated within the cytoplasm of macrophages**
  - Small nodular aggregates of macrophages to classical caseating or non-caseating granulomas containing epithelioid cells and Langhans giant cells
  - Meningeal involvement also demonstrates granulomatous inflammation
  - Walls of blood vessels can become involved, causing focal vascular necrosis and thrombosis, with resulting infarction

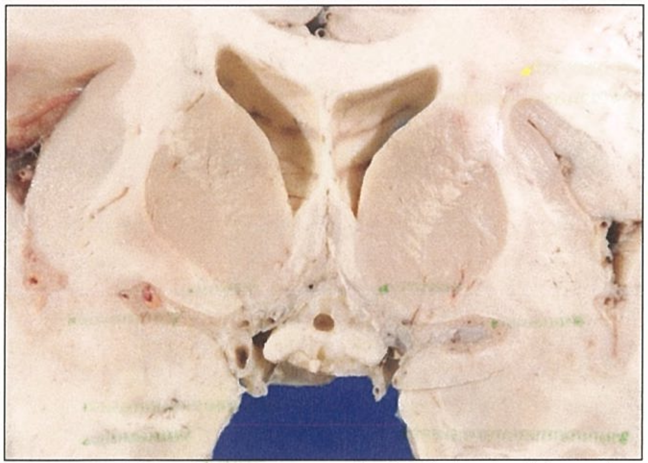
OTHER HIGH YIELD POINTS

- Causative organism: *Histoplasma capsulatum*
- Portal of entry is usually pulmonary, CNS involvement is relatively rare
  - Confusion, seizures, signs of increased intracranial pressure; focal neurologic findings are rare
- Predisposing factors: AIDS, steroids, hematological malignancy, transplantation, solid tumors
- Diagnosis depends on organism identification via staining or culture



Coccidiomycosis showing large round sporangia with thick capsule in leptomeninges, higher power picture given below
Pictures courtesy: Dr. Jared Ahrendsen





Leptomeningeal coccidiomycosis. Man in his fourth decade of life, resident of the northern border of Mexico. He had respiratory symptoms with a diagnosis of pulmonary coccidiomycosis by biopsy. He died due to neurological impairment. At autopsy, an infectious perichiasmatic plastron is identified

COCCIDIODOMYCOSIS

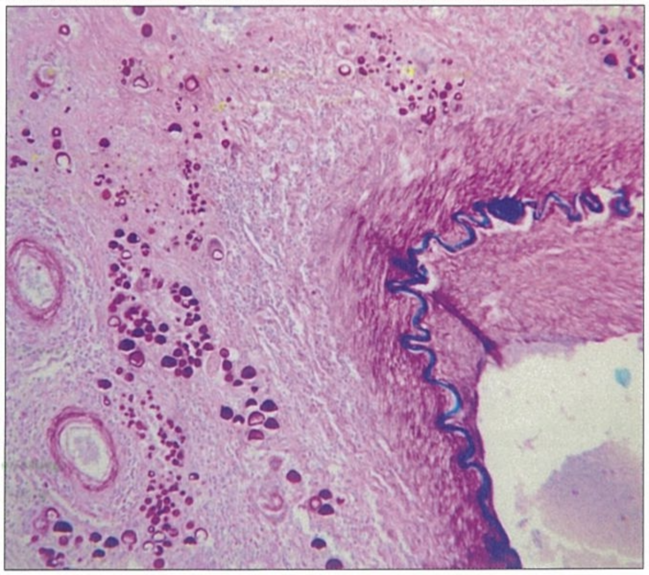
MORPHOLOGY

- Macroscopic:
  - Exudate visible in cerebral sulci or over the base of the brain
  - Thickened and opacified meninges
  - Small granulomas may be visible
  - Scattered small granulomas or abscesses (less common) seen on coronal sections
  - Ischemic lesions, infarcts, or multifocal encephalomalacia may be seen
- Microscopic:
  - Large round sporangia with a thick refractile capsule containing endospores (sporangiospores)
  - Sporangiospores are released into the surrounding tissue when sporangia rupture
  - Visible on H&E, best seen on methenamine silver stain
  - Granulomatous inflammation surrounding sporangia
  - Acute inflammatory response with neutrophils and microabscess formation surrounding sporangiospores

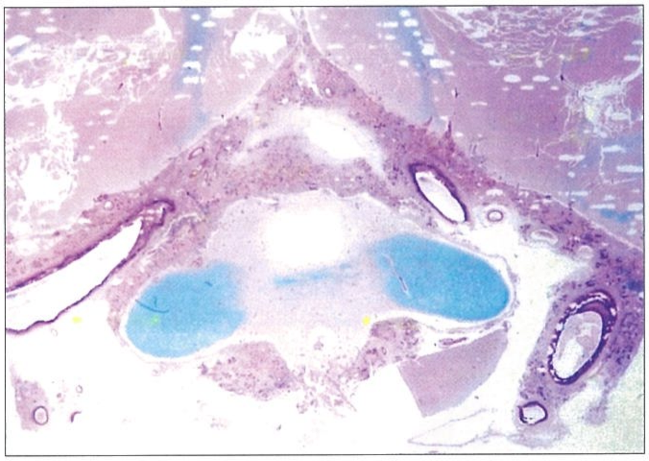
OTHER HIGH YIELD POINTS

- Causative organisms: *Coccidioides* (*immitis, posadasii*)
- Initial pulmonary infection is associated with occupations involving exposure to large amounts of dust
- Hematogenous spread is rare; pregnancy, diabetes mellitus, or immunosuppression are risk factors
- CNS involvement is late, usually terminal
  - Manifests as acute, subacute, or chronic meningitis
  - Transient focal deficits such as aphasia or hemiparesis
  - Sometimes complicated by acute hydrocephalus
  - Spinal involvement with granulomas can produce spinal cord compression

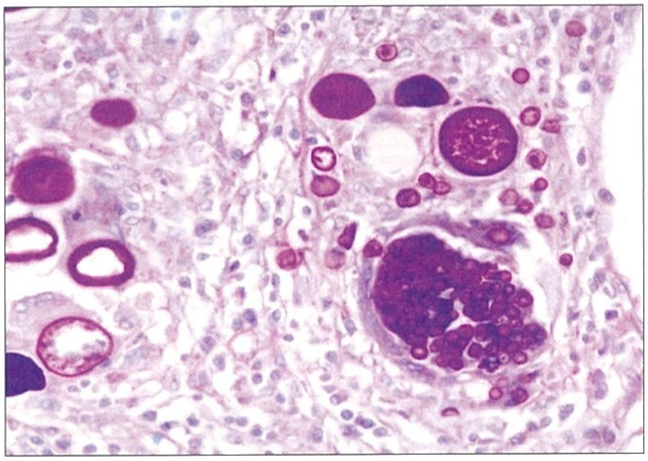
Kluver-Barrera stain (400X), with the presence of microorganisms in the subarachnoid space and located very close to venous and arterial vessels



Kluver-Barrera stain (panoramic photograph) from the above-mentioned autopsy case; there is expansion of the perichiasmatic cysten



Kluver-Barrera staining (1000X), there are spherules of different sizes; there is a multinucleated giant cell with endospores inside



Picture courtesy: Laura Chavez-Macias, MD and Eric Gomez-Apo, MD

BLASTOMYCOSIS

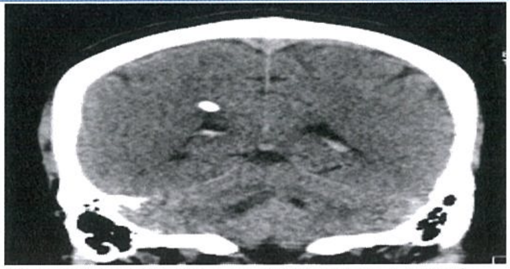
MORPHOLOGY

- Macroscopic:
  - Patchy thickening and opacity of meninges
  - Combination of purulent exudate and fibrosis
  - Hydrocephalus may result
  - Small underlying abscesses and granulomas in subdural space and/ or brain parenchyma
  - Abscesses or granulomas (blastomycomas); solitary or multiple and can occur in any part of the CNS
- Microscopic:
  - Spherical yeast with broad budding, visible on H&E, best seen on PAS or methenamine silver stain
  - Mixed granulomatous and purulent reaction
  - Older abscesses develop a thick collagenous capsule
  - Central caseating necrosis and Langhans-type giant cells, similar to tuberculous granulomas may be seen

OTHER HIGH YIELD POINTS

- Causative organism: *Blastomyces dermatitidis*
- CNS involvement is rare (<5% of cases)
- Hematogenous spread from the lungs
- Most patients also have symptoms of lung disease
- Symptoms and signs vary by disease involvement
  - Meningitis: pyrexia, headache, vomiting, nuchal rigidity, and photophobia
  - Blastomycomas: focal neurologic deficits and evidence of increased intracranial pressure
- Risk does not seem to be increased by immunosuppression or debilitating disease

PARASITIC CNS INFECTIONS

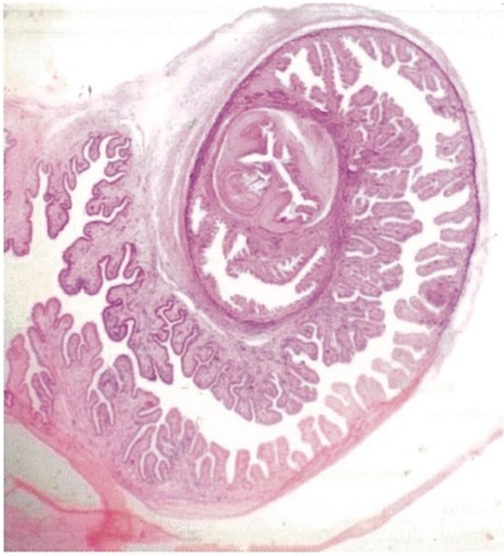


CT scan demonstrating a calcified nodule in a case of cysticercosis

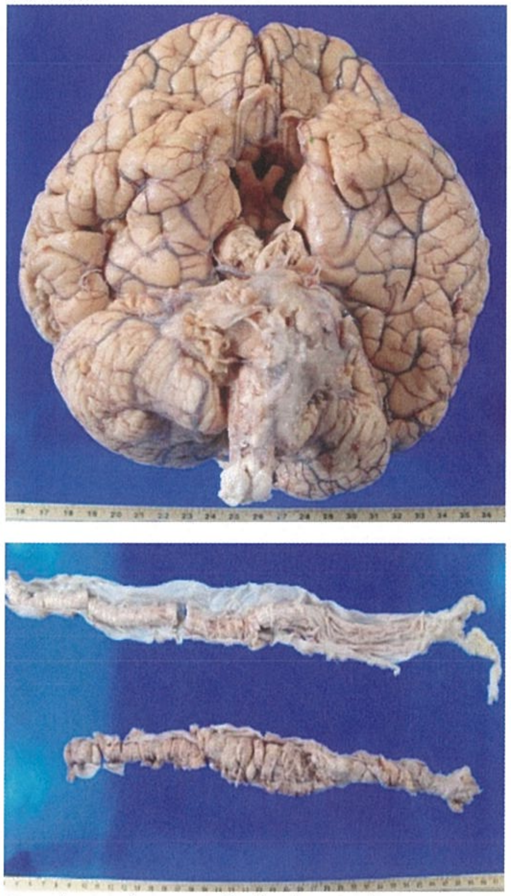
CYSTICERCOSIS

MORPHOLOGY

- Macroscopic:
  - The number of cysts varies from one to several hundred
  - Located in the parenchyma (especially the gray matter), meninges, or ventricles
  - The spinal cord is rarely involved
  - Viable intraparenchymal cysticerci are usually 1-2 cm in diameter and contain a single invaginated scolex; it becomes a firm white fibrotic nodule following degeneration and eventually calcifies
  - Meningeal cysts are small and colorless; they adhere to pia or float freely in subarachnoid space; sylvian fissure in particular is a common location
  - Basal cysts tend to shrink, with thickening and fibrosis of the meninges



Cysticercosis cyst on H&E stain
Radiology and photomicrograph courtesy: Dr. Silvia Hernandez



Gross images demonstrating involvement by neurocysticercosis
Gross pictures courtesy: Dr. Ana Calderon

  - Racemose cysts are large multiloculated grape-like clusters of cysts that lack an invaginated scolex; usually seen in basilar cisterns or within the ventricular system; also fourth ventricle in particular
- Microscopic:
- Each scolex has a rostellum with four suckers and a double row of 22-32 hooklets
- Cyst wall is sparsely cellular and consists of three histologically distinct layers
  - Outer or cuticular layer (eosinophilic and with hair-like protrusions called microtrichia)
  - Middle cellular layer
  - Inner reticular or fibrillary layer which may contain fine mineral granulations
- Surrounding tissue response varies with the life cycle of larvae
  - Minimal reaction when encysted larvae are viable
  - Neutrophils, lymphocytes, macrophages, foreign body giant cells, and eosinophils arrive shortly after the cysticerci die
  - Granulation tissue encloses the inflammatory infiltrate, eventually producing a dense collagenous capsule
- Necrotic tissue and cholesterol clefts may be seen within the lesion
- Old nodules may be entirely fibrotic and mineralization occurs in some cysts
- Granular ependymitis usually seen with ventricular cysticerci
- Degeneration of racemose cysticerci in the ventricles or subarachnoid space may provoke a florid granulomatous inflammatory reaction

OTHER HIGH YIELD POINTS

- Causative organism is *Cysticercus cellulosae* (larval form of *Taenia solium*)
- Most common parasitic infection of the CNS globally
- Leading cause of epilepsy worldwide
- Results from ingestion of food contaminated with *T. solium* ova from infected feces
  - Autoinfection is also possible through regurgitation/ reverse peristalsis and swallowing of intestinal ova in humans already infected with adult *T. solium* worms
- Ova hatch in the small intestine and larvae disseminate to other tissues (brain, eyes, liver, lung, and subcutaneous tissue) where they mature into cysticerci
- Clinical features vary depending on the number and location of cysts
- Focal and generalized seizures, papilledema, headache, vomiting, and ataxia (which may be intermittent), vertigo produced by abrupt movements of the head, focal motor and sensory deficits, dementia, acute hydrocephalus due to obstruction of the ventricular system, **sudden death (occasional)**
- Often discovered incidentally at autopsy

↳ Sindrome de
Bruns

TOXOPLASMOSIS

MORPHOLOGY

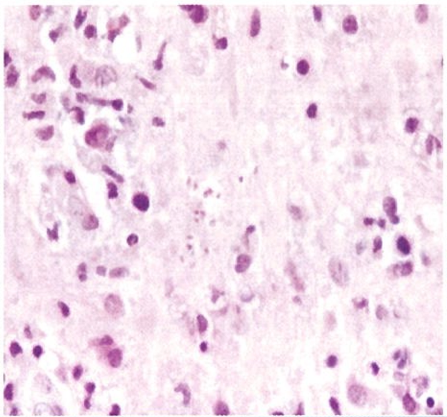
- Macroscopic:
- **Postnatally-acquired cerebral toxoplasmosis**- multifocal necrotic lesions of varying size, associated hemorrhage, older lesions are cystic, basal ganglia often involved, encephalitic process without obvious focal lesions – occasional
- **Congenital toxoplasmosis-** multifocal or confluent **areas of necrosis, particularly in periventricular and subpial regions,** hydrocephalus or even hydranencephaly (secondary to vascular thrombosis), scattered foci of calcification, microcephaly
- Microscopic:
- Postnatally-acquired cerebral toxoplasmosis
  - Intracellular and extracellular tachyzoites are usually abundant
  - Cysts containing large numbers of bradyzoites may occur within, or at the periphery of necrotic areas
  - Both tachyzoites and bradyzoites are visible on H&E, more readily identified and distinguished from other protozoa immunohistochemically
  - Necrotizing abscesses or foci of coagulative necrosis
  - Surrounding mononuclear and polymorphonuclear inflammatory cells, newly formed capillaries, reactive astrocytes, and microglia
  - Scant fibrous encapsulation
  - Less prominent inflammation and absent fibrosis in severely immunocompromised patients
  - **Chronic lesions show cystic spaces containing macrophages and very rare tachyzoites**
  - End-stage (burnt-out) lesions show foci of cavitation and gliosis with surrounding tissue reaction
  - HIV patients who have received combined antiretroviral therapy (cART)
  - Florid inflammation is seen in patients who develop immune reconstitution inflammatory syndrome (IRIS)
  - Vascular findings: perivascular lymphocytic and macrophage infiltrates as well as hemorrhage, intimal proliferation and thrombosis, and fibrinoid necrosis
- Congenital toxoplasmosis
  - **Tachyzoites and cysts can be seen in meningeal exudate,** around the necrotic lesions, and near the ventricular cavities (particularly numerous)
  - Residual cysts can usually be found in mineralized lesions
  - Active lesions show extensive coagulative necrosis
  - Usually associated with lipid-laden macrophages, lymphocytes, and a few neutrophils
  - Eventually tend to undergo mineralization
  - Adjacent brain may contain microglial nodules
  - Inflammatory infiltrate is also present in the leptomeninges
  - Ependymal granulations and gliosis
  - May lead to aqueduct stenosis and obstructive hydrocephalus

OTHER HIGH YIELD POINTS

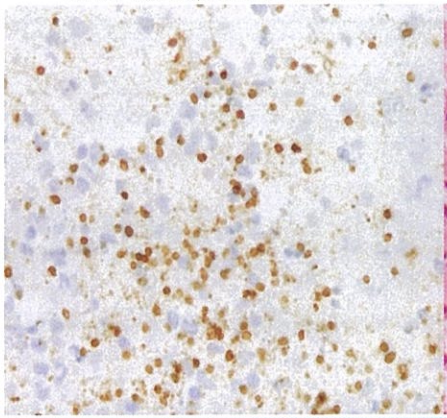
- Causative organism is *Toxoplasma gondii*
- Congenital toxoplasmosis
  - Almost always due to primary maternal infection during pregnancy
  - Transplacental spread of protozoa
  - The risk of congenital infection is greatest during the latter part of pregnancy
  - More severe CNS and eye involvement are seen in congenital infections during earlier months of pregnancy
  - Seizures are often a prominent early feature
  - **Classic triad: hydrocephalus, cerebral calcifications, chorioretinitis** (Seen only in a minority of cases)
- Postnatally-acquired cerebral toxoplasmosis
  - Definitive hosts are domestic cats and other feline species
  - Symptomatic disease in immunocompetent individuals is rare
  - More commonly associated with depression of cell-mediated immunity, particularly in **AIDS (CD4 count <100 cells/microL)**

Variable symptomatology: headaches, drowsiness, disorientation, non-specific features of raised intracranial pressure, and progressive focal neurologic deficits

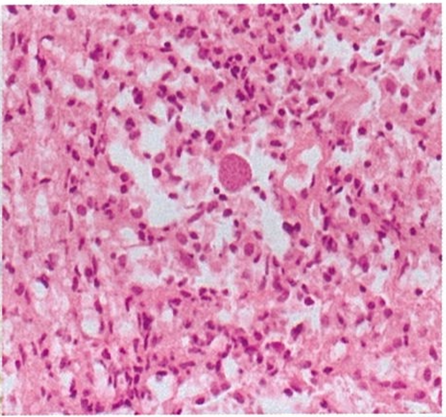
Toxoplasma organisms- They appear smaller than surrounding cells



Immunostain for *Toxoplasma*
Picture courtesy: Dr. Steven Schwartz



H&E stain demonstrating *Toxoplasma* spherule
Picture courtesy: Dr. Bartholomew White



AMEBIASIS

MORPHOLOGY

Macroscopic:

- **Cerebral amebic abscess**
  - Single lesion usually, multiple abscesses occasionally
  - Cortical gray matter, junction of cortex and white matter, or basal ganglia
  - Early: small foci of hemorrhagic softening
  - Progress into necrotic lesions with yellow-green centers
  - Cavitation follows
  - Walls are irregular with no evidence of encapsulation
- **Primary amebic meningoencephalitis**
  - Cerebral edema
  - Hemorrhagic exudate in the meninges
  - Hemorrhagic necrosis involving olfactory bulbs, olfactory tracts, and adjacent parts of the frontal and temporal lobes
- **Granulomatous amebic encephalitis**
  - Cerebral edema
  - Diffuse leptomeningeal exudate
  - Foci of softening, hemorrhage, and necrosis
  - Anterior part of cerebral hemispheres, thalamus, brainstem, and cerebellum

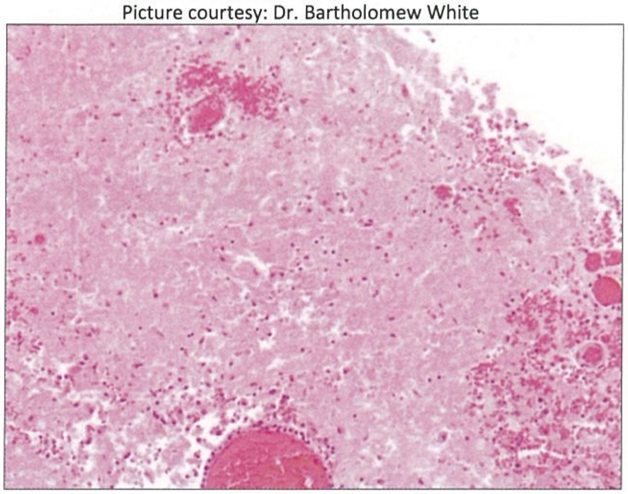
Microscopic:

- **Cerebral amebic abscess**
  - Trophozoites can usually be identified in the abscess wall but may be difficult to identify within central necrotic tissue
  - Spherical to oval in shape, have vacuolated cytoplasm with abundant glycogen and a single nucleus
  - Surrounding parenchyma demonstrates reactive gliosis and an infiltrate of lymphocytes, plasma cells, macrophages, and some neutrophils
- **Primary amebic meningoencephalitis**
  - Amebae are present in the subarachnoid space and in a perivascular distribution within necrotic parenchyma
  - Vesicular nucleus with large central nucleolus helps to distinguish them from macrophages
  - Scant mononuclear inflammatory infiltrate with focal hemorrhage seen in the leptomeninges
  - Extensive necrosis in brain parenchyma
- **Granulomatous amebic encephalitis**
  - Trophozoites and cysts may be found in and around walls of affected blood vessels as well as areas relatively free of inflammation
  - Prominent vesicular nucleus and dense central nucleolus
  - Cysts are surrounded by a double membrane
  - Foci of chronic inflammatory infiltrate around arteries and veins
  - Typically granulomatous, may be necrotizing
  - Chronic inflammation is also seen in leptomeninges

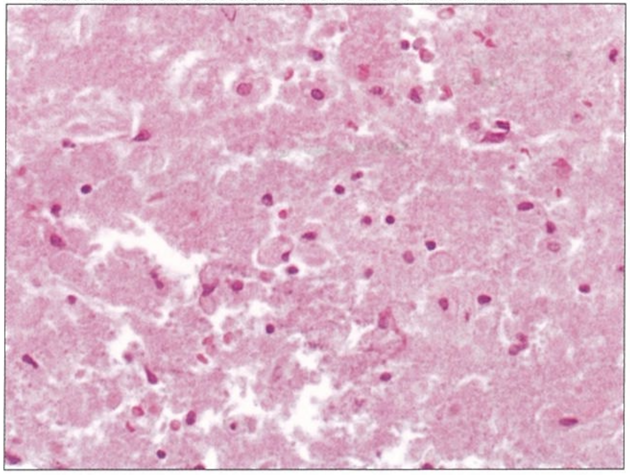
OTHER HIGH YIELD POINTS

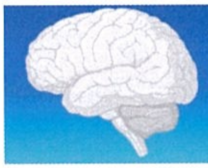
- **Cerebral amebic abscess**
  - The causative organism is *Entamoeba histolytica*
  - Trophozoites invade the brain through hematogenous spread
  - Primary intestinal, pulmonary, or hepatic focus
  - Rare and late complication, usually fatal
  - Non-specific symptoms, severe headaches particularly prominent
- **Primary amebic meningoencephalitis**
  - The causative organism is *Naegleria fowleri*
  - Direct extension into the brain from nasal cavity infection
  - Acute, fulminant, rapidly fatal illness
  - Affects previously healthy children and young adults
- **Granulomatous amebic encephalitis**
  - Causative organisms: *Acanthamoeba* and *Balamuthia* species
  - Hematogenous spread from lower respiratory or skin primary
  - Chronically ill or immunosuppressed patients
  - Headache, fever, stiff neck, focal neurologic abnormalities, and seizures
  - Subacute or chronic course and is usually fatal

H&E stain demonstrating amebic abscess
Picture courtesy: Dr. Bartholomew White



H&E stain demonstrating amebic organisms; note the cytoplasmic vacuoles and red coloration of the nucleus in the ameba





4. INFECTIONS

MALARIA

MORPHOLOGY

- Macroscopic:
  - Cerebral edema
  - Congested leptomeninges
  - Cortex dusky pink due to marked congestion or slate gray due to abundant malarial pigment
  - Petechial hemorrhages in white matter
- Microscopic:
  - Small vessels engorged by parasitized red blood cells
  - Ghost-like appearance with poor staining of hemoglobin
  - Many contain malaria parasites and/or granules of dark malarial pigment (related to hematin)
  - Particularly in gray matter
  - Edema, capillary necrosis, and perivascular hemorrhage are usually evident
  - Petechial or larger hemorrhages most common in white matter; may surround necrotic arteries or veins
  - Foci of softening and gliosis seen in patients with longer survival
  - Parenchymal and meningeal infiltration by lymphocytes and macrophages
  - Dürck granulomas – collections of microglia and astrocytes (microglia contain iron pigment and lipid)

OTHER HIGH YIELD POINTS

- Causative organism: *Plasmodium falciparum*
  - Vector: *Anopheles* mosquito
- CNS involvement in 1-10% of patients
  - Most common in those not immune to the parasite (i.e., children 6 months-4 years of age and foreign visitors to endemic areas)
  - Key event: sequestration of parasitized red blood cells in microvasculature of the brain
- Initial presentation includes fever, severe headache, somnolence, disorientation, backache, photophobia, and vomiting
- Seizures are common, especially in children
- Additional signs and symptoms vary by the affected region(s)
- Rapid progression to coma occurs in the absence of prompt treatment
- Fatal in 20-50% of patients

SCHISTOSOMIASIS

MORPHOLOGY

- Macroscopic:
  - Cerebral disease
    - Miliary granulomas may be scattered throughout
    - Most numerous in cerebral and cerebellar cortex and the deep gray matter
    - Lesions are sometimes solitary, mimicking a tumor
  - Spinal disease
    - Marked swelling of affected cord segments
  - Both cerebral and spinal disease may have granulomas studded over the surface, or agglomerated to form nodules
    - Protrusion from the surface and occasional invasion of the dura seen in the latter
- Microscopic:
  - Ova are visible on H&E
  - Surrounding tissue response varies from nothing to florid granulomatous inflammation with multinucleated giant cells, marked fibrosis, and adjacent gliosis
  - Eosinophils are usually present
  - Focal arteritis in some patients

OTHER HIGH YIELD POINTS

- Causative organisms: *Schistosoma* species
  - *S. japonicum, S. mansoni, S. haematobium*
  - *S. japonicum*: cerebral disease is the most common
  - *S. haematobium*: Spinal cord commonly affected, may cause cerebral disease
    - Lumbosacral segments commonly involved
    - Sometimes inferior thoracic segments are involved as well (*S. mansoni*)
    - More rarely in cervical segments
- The definitive host is human but snails are an intermediate host to develop from miracidia to cercariae
- Enter humans through the skin; maturation and reproduction occur within vasculature
- CNS involvement is uncommon
- Embolization of eggs from the portal mesenteric and pelvis system to the brain and spinal cord is the main route of CNS invasion
  - Pulmonary arteriovenous shunts or portopulmonary anastomosis
  - Retrograde venous flow into the valveless epidural venous plexus of Batson (portal hypertension facilitates this route)
  - Anomalous migration of the adult worms, followed by egg deposition in situ in the CNS (possibly)

VIRAL CNS INFECTIONS

GENERAL FEATURES

CLASSIFICATION

- A combination of the approaches below is generally used for classification and diagnosis
- Course of disease: Acute, subacute or chronic
- Most severely involved/ target tissue
  - Meningitis
  - Poliomyelitis, polio encephalomyelitis
  - Viral leukoencephalopathy
  - Panencephalitis
- Patient age group
  - Fetal
  - Neonatal
  - Child
  - Adult
- Patient immune status
- Etiologic

4. INFECTIONS

ASEPTIC MENINGITIS

MORPHOLOGY

- Macroscopic:
  - No specific abnormalities seen
- Microscopic:
  - Scant lymphocytic infiltrate in the meninges, perivascular space surrounding some superficial cortical blood vessels, and choroid plexus

OTHER HIGH YIELD POINTS

- **Benign**, usually short-lived syndrome of meningeal inflammation
- Occasionally, patients with aseptic meningitis die as a result of a concurrent systemic illness (e.g., viral myocarditis)
- Wide range of viral etiologies
  - Coxsackie B
  - Coxsackie A
  - Herpes simplex virus (HSV)-2
  - Mumps
  - Human immunodeficiency virus (HIV)
  - Lymphochoriomeningitis virus
  - Arboviruses
  - Measles
  - Parainfluenza virus
  - Adenovirus
- Enteroviral infection is the most common cause, with peak incidence during late summer and fall
- Other causes less common
  - Bacterial and other microorganisms
  - Non-infective inflammatory disorders
  - Tumors
  - Drugs

POLIO (POLIOMYELITIS/ POLIOENCEPHALOMYELITIS)

MORPHOLOGY

- Macroscopic:
  - Acute phase
    - Macroscopic lesions not usually seen
    - Vascular congestion, petechial hemorrhages, and focal necrosis may be seen in severe cases, evident in the spinal matter or brain stem
  - Chronic phase
    - Wasting of affected muscles is seen years after the acute phase
    - Thinning and gray discoloration of the corresponding anterior spinal nerve roots
- Microscopic:
  - Distribution of lesions is variable
    - Spinal gray matter is usually involved, particularly **anterior horn cells**
    - Motor nuclei in the pons and medulla, the reticular formation, and deep cerebellar nuclei also show a predisposition to infection
    - Cerebral cortex is usually spared
      - **Exception: precentral gyrus**
  - Acute phase
    - **Neuronophagia**: aggregation of microglia and macrophages around dead neurons; **histologic hallmark of the viral infection of neurons**
    - Clusters of microglia (microglial nodules) mark the site of destroyed neurons for several weeks following resorption
    - Intense inflammation in the leptomeninges and affected gray matter
    - Neutrophils initially, but lymphocytes soon predominate
    - Lymphocytic cuffing of blood vessels
    - Congestion of small blood vessels often seen in the areas of inflammation
    - Associated perivascular hemorrhage may be seen
    - Occasional associated focal necrosis
    - Widespread inflammation involving the spinal gray matter, brain stem, hypothalamus, subthalamic and dentate nuclei, along with necrotizing lesions in the dorsomedial pons and medulla, can be seen in infection with enterovirus 71.
  - Chronic phase
    - Obvious loss of motor neurons
    - Atrophy and fibrosis of nerve roots
    - Scant residual inflammation

OTHER HIGH YIELD POINTS

- Caused by members of the genus *Enterovirus*
- Spread through fecal-oral transmission, facilitated by crowding and poor sanitation
  - CNS infection is due to hematogenous spread: initial intestinal infection and replication → primary viremia with spread to reticuloendothelial system → further replication with secondary viremia → enter CNS
- The incidence of poliomyelitis due to polioviruses has sharply declined in developing countries due to vaccine development

  - Outbreaks still occur in a few developing parts of the world and in communities that refuse vaccination
- Infections are still seen in vaccinated communities due to:
  - Other enteroviruses (e.g., Group A coxsackie viruses and enteroviruses)
  - Arboviruses (e.g., Japanese encephalitis virus, West Nile virus, tick-borne encephalitis virus)
  - Rare reversion to neurovirulence of attenuated vaccine-related strains of poliovirus
- Minor nonspecific illness at the time of primary viremia
  - Gastrointestinal upset, mild pyrexia, headache, and general malaise
- A small percentage of patients develop paralytic polio encephalomyelitis some days after the resolution of the initial disease
  - Usually heralded by pyrexia, headache, vomiting, neck stiffness, and irritability in children
  - Symptoms may be less pronounced in adults
  - Muscle pain or stiffness may occur before the development of paralysis
  - Paralysis is typically asymmetric, with lower limbs more often involved than upper limbs
  - Cranial nerve palsies seen in bulbar disease
  - Cardiac arrhythmias and abnormal patterns of breathing are seen in involvement of the reticular formation of upper limbs or trunk
- Complications
  - Post-polio syndrome: increasing weakness or muscular atrophy developing many years later in survivors with no other neuromuscular disease; cause not known
  - Chronic enteroviral meningoencephalitis: rare complication in patients with depressed humoral immunity, due to X-linked agammaglobulinemia or combined variable immunodeficiency

ARBOVIRUSES

MORPHOLOGY

- Macroscopic:
  - Moderate congestion and edema
  - Petechial hemorrhages
  - Regions most severely affected vary by specific viral etiology
    - Western and Eastern equine encephalitis: basal ganglia, thalamus, brainstem
    - Japanese encephalitis: thalamus, substantia nigra, brainstem, spinal cord
    - West Nile fever: thalamus, cerebellum, substantia nigra, pons, medulla, and spinal cord, with predominantly gray matter involvement
    - St. Louis encephalitis: midbrain, thalamus
  - Material should be taken at autopsy or biopsy for electron microscopy and viral culture if infection is suspected
    - Abundant viral antigen is demonstrable in neurons
- Microscopic:
  - Leptomeningeal, perivascular, and parenchymal infiltration
  - Predominantly lymphocytes and microglia or macrophages
  - Gray matter shows neuronophagia and microglial nodules as well as perivascular cuffs of mononuclear inflammatory cells (especially lymphocytes) and perivascular hemorrhages
    - No distinctive nuclear or cytoplasmic inclusions
  - White matter shows perivascular inflammation associated with focal necrosis of myelinated fibers
  - Thrombosed small blood vessels
  - Large regions of necrosis (rare)

OTHER HIGH YIELD POINTS

- Arthropod-borne small-enveloped RNA viruses
- Vector is usually mosquito or tick
- Viral replication at the site of host inoculation → spread to regional lymph nodes and other lymphoreticular tissue and proliferates (primary viremia) → hematogenous dissemination (secondary viremia) to systemic tissues
- A small proportion of infections result in hemorrhagic fever or encephalitis
- Four families, each with some viruses that cause encephalitis
  - Togaviridae: Eastern equine encephalitis, Western equine encephalitis, Venezuelan equine encephalitis
  - Reoviridae: Colorado tick fever virus
  - Flaviviridae: St. Louis encephalitis, Japanese encephalitis, Murray Valley encephalitis, West Nile virus, Rocio virus
  - Bunyaviridae: California serogroup viruses (especially La Crosse virus), Tahyna virus, Jamestown Canyon virus, Rift Valley fever virus
  - Toscana virus is a rare cause of encephalitis; a major cause of meningitis
- The incubation period is usually <1 week but can be up to 3 weeks
- Acute presentation includes fever (sometimes marked), malaise, and myalgias

- Neurologic signs are nonspecific
  - Headache, vomiting, diarrhea
  - Altered level of consciousness, disorientation
  - Flaccid or spastic paralysis
  - Seizures
- Progression to coma may occur rapidly
- Morbidity and mortality greatly vary depending on the infectious agent
  - Eastern equine encephalitis has a mortality of 50-75%; 90% of survivors have persistent neurologic disability
  - Japanese encephalitis has a mortality of up to 50%; with a high proportion of survivors having persistent neurologic disability
  - West Nile virus has a mortality of 3-15% (higher in the elderly); 50-75% of survivors have residual neurologic disability
  - Other arboviruses range in mortality from <1% to over 10%
  - St. Louis encephalitis: less than 5% mortality; approximately 25% of survivors have persistent neurologic disability
- **Serologic tests** or **isolation of virus or specific viral RNA from CSF** usually determines precise viral etiology

MEASLES AND SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE)

MORPHOLOGY

Macroscopic:

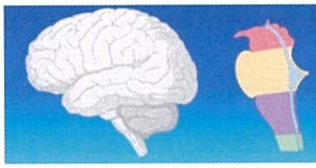
- Measles inclusion body encephalitis
  - Usually normal
  - May be foci of softening and discoloration
- Subacute sclerosing panencephalitis
  - Often normal
  - Moderate to marked brain atrophy in cases of longer duration
  - White matter may have an abnormally firm texture and a mottled gray appearance in cases of longer duration

Microscopic:

- Measles inclusion body encephalitis
  - Occasional or numerous foci of hypercellularity
  - Occur in any part of the brain
  - **Eosinophilic inclusion bodies within many neurons** as well as some astrocytes and oligodendrocytes
    - Intranuclear and intracytoplasmic
    - Cytoplasmic inclusions are less well-defined
    - Readily seen on H&E; can also be demonstrated with immunohistochemistry or by electron microscopy
  - Reactive astrocytes, microglia, and rare multinucleated cells
- Subacute sclerosing panencephalitis
  - Leptomeningeal, perivascular, and parenchymal infiltration by lymphocytes (predominantly T cells) and microglia
  - Distribution and severity of lesions are variable
    - Cerebral cortex, white matter, basal ganglia, and thalamus usually involved
  - Gray matter: inflammation, gliosis, loss of neurons, occasional neuronophagia, and sparse sharply-defined, eosinophilic intranuclear inclusions with a surrounding halo
    - Same inclusion bodies as in measles inclusion body encephalitis, also demonstrated by immunohistochemistry
    - Alzheimer-type neurofibrillary tangles, sometimes numerous, can be seen in the cerebral cortex and hippocampus of patients with a disease duration of several years
  - White matter: severe gliosis, **predominantly perivascular inflammation**, loss of myelinated fibers (usually patchy, some cases show extensive loss)

OTHER HIGH YIELD POINTS

- *Morbillivirus*: enveloped, single-stranded, negative-sense RNA virus in the *Paramyxovirus* family
- Acquired by inhalation of infected fomites
- Highly contagious
- Usually causes a short-lived febrile disease and a characteristic maculopapular rash
- CNS involvement commonly produces an aseptic meningitis or acute disseminated encephalomyelitis (ADEM)
- Subacute/ chronic infective encephalitis is much less common
  - Measles inclusion body encephalitis: within months of the initial systemic infection; patients with impaired cell-mediated immunity
    - Seizures, confusion, variety of neurologic deficits, coma (later)
    - Usually fatal within a few weeks of onset
  - Subacute sclerosing panencephalitis: several years following initial systemic infection; patients without any immunologic impairment
    - Age of onset: 5-15 years
    - More likely if initial exposure occurs at <18 months of age
    - Risk reduced 10- to 20-fold by measles vaccination
    - Four distinct clinical stages
      - I: intellectual impairment and behavioral abnormalities
      - II: repetitive, symmetric myoclonic jerks every 5-10 seconds
      - III: increasing mental deterioration, development of various combinations of ataxia, spasticity, choreoathetosis, dystonia, and gradual disappearance of myoclonus
      - IV: stupor, autonomous disturbances, coma, and eventually death
    - Course of disease is variable
      - Death within months or intermittent progression
      - Survival over 10 years well documented



HERPES SIMPLEX VIRUS

MORPHOLOGY

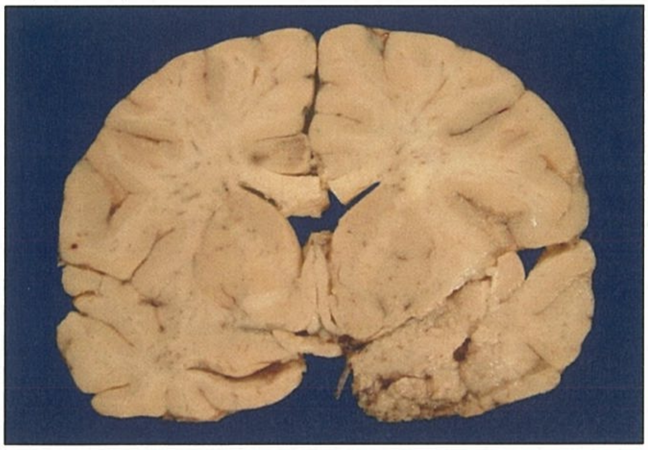
- Macroscopic:
  - Herpes simplex encephalitis
    - Acute phase
      - **Hemorrhagic necrosis involving the temporal lobes**
        - The insulae, cingulate gyri, and posterior orbital frontal cortex are also involved to varying extents
        - **Atypical herpes simplex encephalitis**: involvement of the brainstem, much less frequent
        - Lesions are often somewhat asymmetric
      - Obvious congestion
      - May appear macroscopically normal in very early disease
    - Chronic phase
      - Affected regions are shrunken with cavitation and yellow-brown discoloration
  - Neonatal HSV encephalitis
    - Swollen, with generalized softening and variable congestion and hemorrhage
    - **Severe cystic encephalomalacia may be seen in intrauterine infection**
- Microscopic:
  - Herpes simplex encephalitis
    - **Acute phase**
    - Earliest lesions show a moderate number of lymphocytes and macrophages within the leptomeninges, with relatively scant inflammation within the underlying parenchyma
    - Involve both the cortex and white matter
    - Affected neurons tend to have slightly hyper eosinophilic cytoplasm and pyknotic/disintegrating nuclei → pseudo ischemic stage
    - Glia and endothelial cells may also show these changes
    - Nuclear inclusions present in neurons, astrocytes, and oligodendrocytes
    - Subset of larger cells show homogeneous eosinophilic inclusions; Cowdry A, "owl's eye" inclusions
    - Infected oligodendrocytes show violaceous viral inclusions with beading of the nuclear membrane
    - **Later lesions** are largely necrotic
    - Diffuse permeation of necrotic parenchyma by neutrophils
    - Predominantly cortical but may extend into the white matter
    - Perivascular infiltration by lymphocytes, some highly activated
    - Meningeal infiltration both neutrophils and lymphocytes, may be intense
    - Profuse microglial influx
    - Neuronophagia, microglial nodules
    - Nuclear inclusions are sparse at this stage
    - Viral antigen readily demonstrable by immunohistochemistry, up to approximately 3 weeks after onset of encephalitis
    - Chronic phase
    - Replacement of normal gray and white matter by cavitated glial scar tissue
    - Occasional meningeal and parenchymal clusters of lymphocytes may be seen
  - Chronic granulomatous herpes simplex encephalitis
    - Very rare, occurs in children with previous acute herpes encephalitis, sometimes after an intervening symptom-free period of months or years
    - Patchy cortical and leptomeningeal infiltrate
    - Lymphocytes and scattered, well-circumscribed granulomas
    - Epithelioid macrophages and giant cells, with surrounding lymphocytes, macrophages, and plasma cells
    - Foci of necrosis and mineralization
    - HSV viral DNA still detectable by immunohistochemistry or PCR
  - Necrotizing myelopathy
    - Rare, caused by both HSV-1 and HSV-2
    - Extensive necrosis and inflammation involving spinal gray and white matter
  - Neonatal HSV encephalitis
    - No site predilection, can involve gray and white matter in the cerebrum, cerebellum, and brainstem
    - Otherwise, microscopically identical to adult infection

OTHER HIGH YIELD POINTS

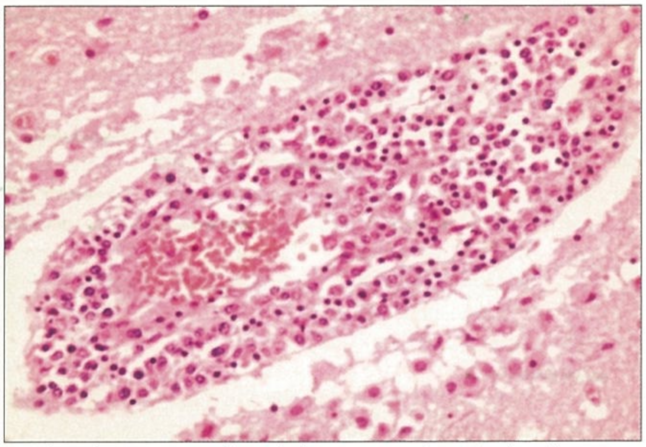
- Relatively large, enveloped, double-stranded DNA viruses
- One of the most common forms of acute necrotizing encephalitis

  - Caused by **HSV-1**, which is spread by direct contact with infected secretions
    - Usually from **orolabial vesicles ("cold sores")**
- Patients present with a combination of nonspecific features of encephalitis and focal neurologic signs
- No treatment: progresses rapidly over a few days and is usually fatal
  - Some patients survive, with abnormalities, memory disturbances, and other neurologic deficits of varying severity
- With treatment: mortality and morbidity fall substantially
  - Approximately 20% of patients still die
  - Risk greatest in the elderly and those with severely depressed levels of consciousness at the start of treatment
- **PCR can be used to detect viral DNA during either acute or chronic stages**
- Neonatal HSV differs in pathogenesis and clinical presentation
  - Most cases due to HSV-2
    - Approximately 15-20% of neonatal HSV infections due to HSV-1, predominantly acquired postnatally
  - Acquired during delivery by contact between the fetus and infected maternal genital lesions; can also be acquired in utero
    - Primary maternal HSV-2 infection during pregnancy and prolonged rupture of membranes in a woman with active genital infection are particular risk factors
  - Disease confined to skin, eyes, and mouth in approximately 45% of cases
    - Vesicular skin lesions, keratoconjunctivitis
  - Encephalitis, with or without other areas of involvement, is present in approximately 35% of cases
    - Presents nonspecifically, with poor feeding, irritability, lethargy, and seizures
  - Mortality is approximately 15% with treatment, and nearly 50% of survivors develop normally
  - Widely disseminated disease, usually involving the brain, liver, and adrenal glands, is present in approximately 20% of cases
  - Mortality is much higher, approximately 50%, but approximately 85% of survivors develop normally

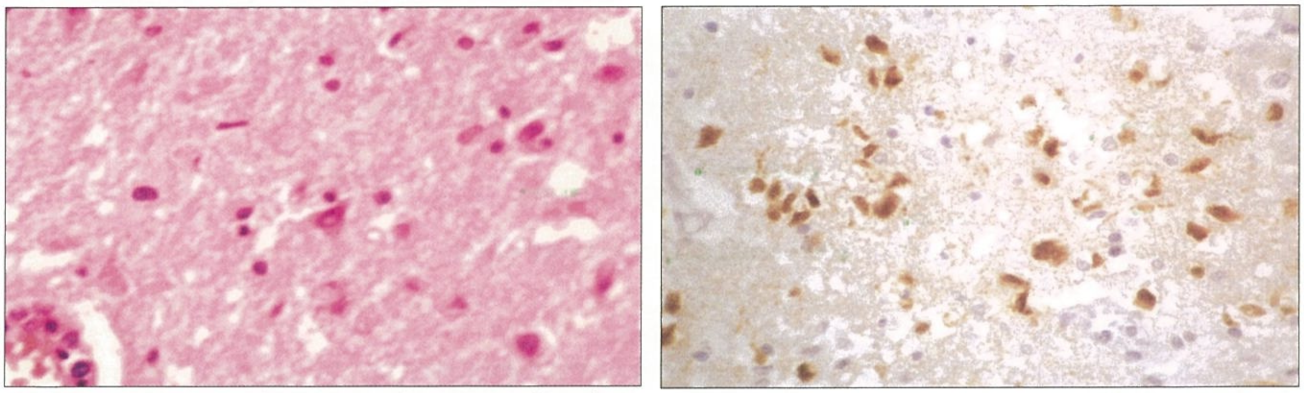
Herpetic encephalitis: Girl with manifestations of a few days of evolution, who died with the clinical diagnosis of acute cerebral infarction



Coronal section of the brain with the presence of bilateral and asymmetric necrotic involvement of the left cingulate gyrus and the right temporal lobe



H&E (100x), microscopically with the presence of reactive lymphocytes with a perivascular arrangment



H&E and anti-herpesvirus IHC (400X), Cowdry body type A in the nucleus of an infected neuron

Picture courtesy: Laura Chávez-Macías, MD, and Erick Gómez-Apo, MD

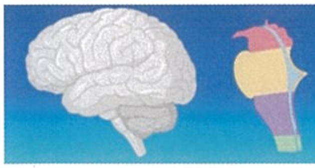
VARICELLA-ZOSTER VIRUS

MORPHOLOGY

- Macroscopic:
  - Varicella meningoencephalitis
    - Near-normal gross appearance in most early-stage cases of meningitis and encephalitis
    - Congestion/hyperemia, edema, and possible focal petechiae may been seen
    - Absence of meningeal purulent exudate
    - Foci of gray matter softening in some cases of late-stage cases
    - White matter lesions can also be seen
  - Fetal and neonatal infection
    - Cerebral cortical atrophy
    - Microcephaly
    - Hydrocephalus
- Microscopic:
  - Varicella meningoencephalitis
    - Typically necrotizing and associated with perivascular and interstitial infiltration by lymphocytes and macrophages
    - Brainstem encephalitis: neuronophagia and microglial nodules tend to be prominent
    - Parenchymal infection: necrotizing or granulomatous vasculitis involving small or large intracranial blood vessels
    - Resulting infarcts and hemorrhages present
    - Intranuclear viral inclusions
  - Zoster intracranial vasculopathy and vasculitis
    - Necrotizing or granulomatous vasculitis involving small or large intracranial blood vessels, but in the absence of parenchymal infection
  - Fetal and neonatal infection
    - Foci of cystic degeneration, glial scarring, and microcalcification
    - Inflammatory infiltrates may be present
    - Active necrotizing infection with viral inclusions and antigens very rarely present

OTHER HIGH YIELD POINTS

- CNS involvement may occur during primary infection (varicella) or recrudescent disease (herpes zoster)
  - Varicella: presumed upper respiratory infection → primary viremic spread to reticuloendothelial system → secondary viremia → systemic spread with typical manifestations of chickenpox
  - Herpes zoster: latent infection in dorsal root ganglia, trigeminal ganglia, or both → reactivation usually manifesting as shingles
    - Often occurs without an obvious precipitating event
    - Recognized risk factors include cancer, lymphoma (especially Hodgkin's disease), ionizing radiation, and immunosuppression
- Diseases associated with varicella:
  - Cerebellitis
    - Complicates approximately 1 in 4,000 cases of chicken pox
    - Usually benign and short-lived
    - Meningism and ataxia
  - Meningoencephalitis
    - Less common
    - Seizures and impaired consciousness
    - May precede or follow the development of the skin rash
    - Most patients make a good recovery
    - A small percentage die during acute illness or suffer permanent neurologic disability
  - Reye syndrome
    - Can be precipitated by the ingestion of salicylates
    - Severe headache, vomiting, and seizures, often progressing to coma
    - Fatal in approximately 20% of cases
    - Autopsy will show microvesicular steatosis of the liver and cerebral edema
- Diseases associated with herpes zoster:
  - Encephalitis
    - Altered mentation, seizures, and variable neurologic deficits
    - Visual or bulbar symptoms may predominate depending on the pattern of infection
  - Myeloradiculitis
    - Presenting neurologic symptoms usually ipsilateral to the rash



        - Paralysis more prominent than sensory loss
    - Both encephalitis and myeloradiculitis usually occur in immunocompromised individuals
        - Usually preceded by a zosteriform skin rash 1-2 weeks prior
    - Vasculopathy and vasculitis
- Fetuses and neonates can develop embryopathy or neonatal varicella
    - Embryopathy: syndrome of limb hypoplasia, CNS abnormalities (see above), cicatricial skin lesions, and ocular defects (chorioretinitis, cataracts, microphthalmia, optic atrophy)
    - Neonatal varicella: usually severe infection with multiple organ involvement

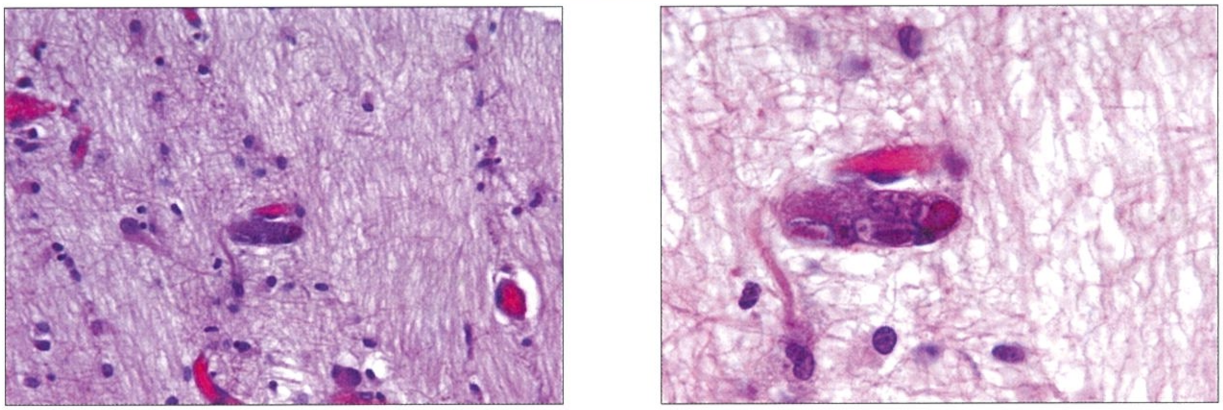
CYTOMEGALOVIRUS

MORPHOLOGY

- Macroscopic:
    - CMV encephalitis and myeloradiculitis
        - Highly variable
        - Low-grade microglial nodule encephalitis (MGNE): near-normal gross appearance in most cases
        - Congestion/hyperemia with absence of meningeal purulent exudate
        - Edema, with possible focal petechiae
        - Necrotizing encephalitis: large areas of cystic encephalomalacia resembling infarcts
        - Ventriculoencephalitis: "sugar icing"-like material lining the ventricular surfaces, with hemorrhagic necrosis of adjacent brain parenchyma
    - Congenital CMV
        - Microcephaly, microgyria, porencephalic cysts, hydrocephalus, and periventricular calcification can be seen in survivors of acute neonatal illness
- Microscopic:
    - CMV encephalitis and myeloradiculitis
        - Low-grade microglial nodule encephalitis (MGNE): widespread low-grade inflammation, with microglial nodules and perivascular lymphocyte cuffing
        - MGNE is non-specific and is a feature of many opportunistic infections
        - Cytomegalic cells are seen within the microglial nodules or without any associated inflammation
        - Severe necrotizing encephalitis: cytomegalic cells present within extensive necrotic foci
        - Ventriculoencephalitis: inflammation and necrosis present within the ependymal and subependymal tissue, with prominent cytomegalic cells; isolated cytomegalic cells can also be seen elsewhere in the brain parenchyma, often with minimal surrounding inflammation
        - Meningoradiculitis and myelitis: chronic inflammatory vasculitis with microthrombi, in and around nerve roots
        - Cytomegalic cells can also rarely be seen within microvascular endothelial cells
        - Foci of demyelination can also be present
    - Congenital CMV
        - Necrotizing encephalitis or ventriculoencephalitis
        - Infiltration by lymphocytes and macrophages
        - Microglial nodules
        - Typical cytomegalic inclusion cells
        - Neurons, glia, endothelial cells
        - Immunohistochemistry or in-situ hybridization can be used to further visualize infected cells

OTHER HIGH YIELD POINTS

- CMV encephalitis and myeloradiculitis
    - The most common viral opportunistic infection of the CNS in patients with acquired immunodeficiency syndrome (AIDS)
        - Present in 15-20% of autopsies of AIDS patients
- Congenital CMV
    - Due to the transplacental spread of the virus in most cases
        - Occasionally acquired postnatally by contact with infected genital secretions, saliva, or breast milk
    - The risk of fetal transmission is approximately 40% during primary maternal infection, <2% during recrudescent maternal disease
    - The risk of fetal complications is highest when infection occurs during the first trimester
    - 10-15% of infected neonates develop symptomatic infection
        - Hepatosplenomegaly with liver dysfunction and consumptive coagulopathy, microcephaly with intracranial calcifications, and chorioretinitis
    - Careful examination of "asymptomatic" cases often discloses minor neurologic impairment, particularly sensorineural hearing loss)
    - Up to 30% of infants die during the acute illness
    - Most survivors have residual neurologic defects
    - Intellectual insufficiency, microcephaly, learning difficulties, seizures, sensorineural hearing loss, chorioretinitis, and optic atrophy



CMV, note the viral inclusions in cell nuclei. Pictures courtesy: Dr. Bartholomew White

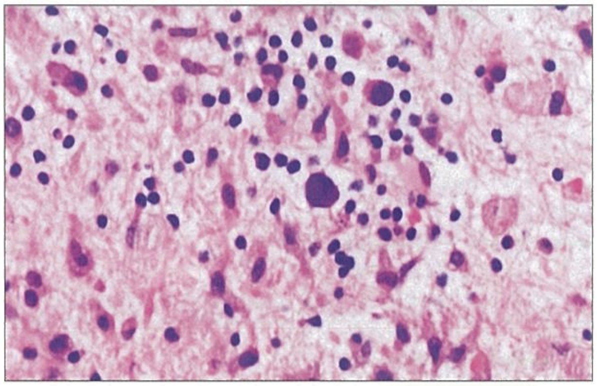
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

MORPHOLOGY

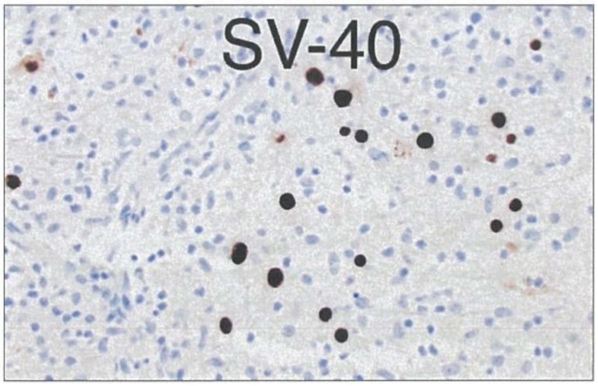
- Macroscopic:
  - Asymmetric pitting by small foci of gray discoloration mixed with large confluent areas of abnormal parenchyma, which may be centrally necrotic
  - **Tend to be most numerous in white matter**, and also involve the cerebral cortex and deep gray matter
  - The cerebellum, brainstem, and spinal cord may also be involved
- Microscopic:
  - Multiple foci of demyelination
    - Ranging from small and rounded to confluent and irregular
    - Occasional central necrosis
    - Moderate numbers of foamy macrophages but only scant perivascular lymphocytes
    - Lymphocytic infiltrates may be commoner in PML associated with AIDS
    - May confer a slightly better prognosis
  - **Homogenous amphiphilic inclusions largely fill the nuclei, which are also enlarged, of oligodendrocytes**
    - Seen towards the periphery of the foci of demyelination
    - Consist of closely packed polyomavirus particles
    - Very large astrocytes with bizarre, pleomorphic, hyperchromatic nuclei
    - Mitoses are rare and may appear atypical
    - **Easily distinguished from a neoplasm by the relatively low cellularity and the presence of viral inclusions**
  - PML involving the cerebellum:
    - Accumulations of cells with large vesicular nuclei and central nucleoli in the granule cell layer
  - **Immunohistochemistry and in situ hybridization both can be used to visualize the virus**

OTHER HIGH YIELD POINTS

- Caused by the **John Cunningham (JC) polyomavirus**
  - Infection in humans is generally asymptomatic
- Thought to result from reactivation of the latent JC virus within the CNS or in peripheral tissues, usually as a result of impaired cell-mediated immunity
  - Most frequently identified in patients with AIDS
  - Other settings include immunosuppressant medications that cause CD4 T-cell lymphoma, rheumatologic disorders, cancer, and status-post transplantation
- Presents with focal neurologic deficits including dysarthria, limb weakness, visual disturbances, ataxia, personality changes, and occasionally seizures
- Usually progresses relentlessly over a few months
  - Increasing neurologic impairment, dementia, and eventually death
- Treatment of the cause of the underlying immunosuppression can lead to remission
  - Immune reconstitution inflammatory syndrome (IRIS) following plasma exchange (in cases of patients on natalizumab) or the initiation of highly active antiretroviral therapy (HAART, in cases of patients with HIV/AIDS) can result in exacerbation of the disease
  - Treated with steroids



Homogenous amphiphilic inclusion filling the oligodendroglia nuclei
Picture courtesy: Dr. Jared Ahrendsen



SV-40 immunostain showing positive staining

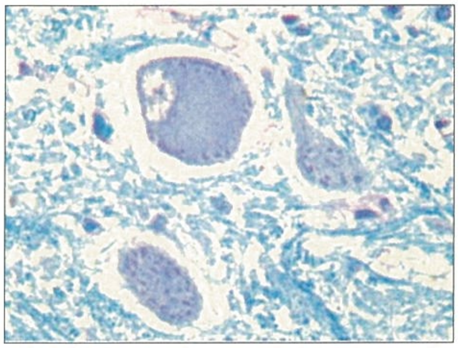
RABIES VIRUS

MORPHOLOGY

- Macroscopic:
  - Usually macroscopically normal
  - The brain and spinal cord may appear swollen
- Microscopic:
  - Findings of a widespread polioencephalomyelitis
    - May be a striking disparity between the abundance of virus and the limited degree of inflammation
    - Babès nodules: clusters of microglia that remain after neuronal destruction
  - **Classic histologic feature: Negri bodies → sharply delineated, round or oval, eosinophilic inclusions in the neuronal cytoplasm** (Inclusions occur in most parts of the CNS; however, easiest to find in Purkinje cells, hippocampal pyramidal cells, and brainstem nuclei)
  - Lyssa bodies → less well-defined (although ultra-structurally similar) eosinophilic inclusions also present in neuronal cytoplasm (same distribution as Negri bodies)

OTHER HIGH YIELD POINTS

- RNA virus in the Rhabdovirus family
- Usually transmitted by the bite of a rabid animal
  - Dogs (rare in developed countries due to vaccination), cats, foxes, skunks, raccoons, lynxes, wolves, jackals, mongooses, and bats
  - Silver-haired/eastern pipistrelle bat (since 1990, the most frequent cause of fatal rabies in the United States)
- Aerosol transmission is a recognized but rare consequence of visiting caves populated by infected bats
- Virus replicates within skeletal muscle at the site of inoculation → taken up by axons and transported centripetally to the CNS → virus replicates within the CNS and spreads through the spinal cord and brainstem to the cerebrum and cerebellum
- Infection consists of several stages
  - Incubation period
    - Ranges from 10 days to 1 year, very rarely longer
    - Shorter in children than adults
    - Varies according to the proximity of the site of inoculation to the CNS (Most rapid after bites to the head)
  - Prodrome
    - 2-10-day period of headache, fever, malaise
    - Occasionally pain or paresthesia at the site of the bite
  - Acute neurologic disease
    - Lasts 2-7 days
    - One of two forms, which may overlap
    - "Furious" rabies (more common, agitation, insomnia, aggressive behavior, hallucinations, **hydrophobia**, and brainstem dysfunction (e.g., dysphagia, dysarthria, nystagmus, and cardiorespiratory disturbances)
    - "Dumb" rabies **Paralysis of one or more limbs** (sometimes ascending paralysis simulating Guillain-Barré syndrome), sensory loss, and incontinence
  - Terminal stage
    - Complications during this stage include syndrome of inappropriate antidiuretic hormone secretion (SIADH), diabetes insipidus, cardiac and respiratory failure
    - Progresses to stupor, coma, and death



Negri bodies. Picture Courtesy: Martha Tena-Suck, MD

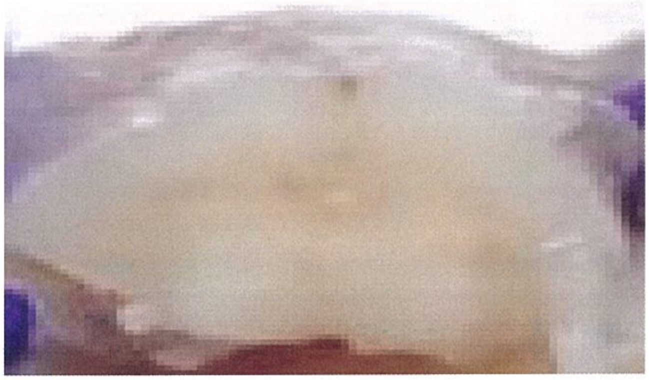
PRIMARY HIV ENCEPHALOPATHY (HIVE)

MORPHOLOGY

- Macroscopic:
  - Direct HIV infection of the CNS
    - May appear grossly normal
    - Diffuse atrophy with modest ventriculomegaly and ill-defined gray discoloration of the centrum semiovale
  - Vacuolar myelopathy
    - Vacuolization of the spinal white matter in the posterior columns and lateral corticospinal tracts
    - Most pronounced in the thoracic segments
  - Necrotizing leukoencephalopathy
    - Vacuolating lesions may be seen macroscopically
  - Pediatric HIV infection of the CNS
    - Same findings as adult HIV encephalitis
    - Dystrophic parenchymal and angiocentric calcification
- Microscopic:
  - Direct HIV infection of the CNS
    - Findings of microglial nodular encephalitis
    - Leukoencephalopathy with patchy demyelination and variable gliosis of white matter
    - Often with associated gliosis of deep central gray matter
    - **Multinucleated giant cells**
    - Sufficiently diagnostic for HIV infection if other causes of granulomatous inflammation with giant cells have been ruled out
    - Usually pericapillary
    - Scant cytoplasm (morulae) or abundant cytoplasm (true giant cells)
    - HIV antigen can be demonstrated within these cells using immunohistochemistry
    - **HIV antigen may be demonstrable in microglial cells, even without characteristic "giant cell" morphology**
  - Vacuolar myelopathy
    - Breakdown of myelin accompanied by accumulations of debris-containing macrophages
    - Breakdown of axons occurs at later stages
  - Necrotizing leukoencephalopathy
    - **Intense perivascular macrophage and lymphocyte infiltration**
    - High levels of HIV detectable within the CNS
  - Pediatric HIV infection of the CNS
    - Prominent perivascular chronic inflammatory infiltrates
    - Dystrophic parenchymal and angiocentric calcification

OTHER HIGH YIELD POINTS

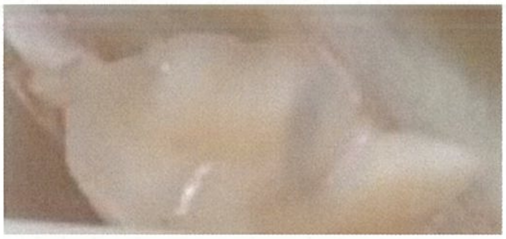
- Retrovirus of the *Lentivirus* family
  - Positive strand RNA virus
- Transmission occurs through contact with infected bodily fluids
  - Vaginal or anal intercourse
  - Intravenous drug injection
  - Vertical transmission from infected mother to child during birth
  - Healthcare or occupational exposure (rare)
  - Blood transfusion (very rare)
- Resides within infected macrophages and microglia within the CNS
  - Occurs even while blood levels of HIV are essentially undetectable
  - Represents a reservoir where systemic re-infection may occur
- CNS infection clinically presents with neurocognitive impairment
  - Asymptomatic early stage
  - Mild-intermediate stage
    - Impaired concentration, memory loss, confusion
    - Apathy, agitation, hallucinations, withdrawal
  - HIV-associated dementia (HAD)
    - Symptoms of dementia, psychosis
    - Synonyms include: HIV-associated neurocognitive disorder (HAND), HIV encephalitis (HIVE), and AIDS dementia complex
- Treated with highly active antiretroviral therapy (HAART)
  - Asymptomatic patients: reduces the incidence of symptomatic dementia
  - Patients with dementia: delays neurologic progression, leading to variable recovery
- Prognosis depends on the stage of disease at the time of HAART treatment



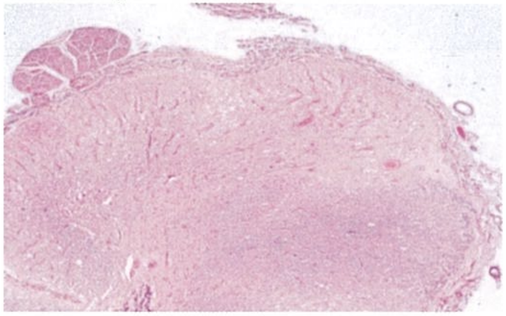
HUMAN T CELL LEUKEMIA/LYMPHOTROPIC VIRUS-1 (HTLV-1)-ASSOCIATED MYELOPATHY (HAM) (TROPICAL SPASTIC PARAPARESIS)

MORPHOLOGY

- Macroscopic:
  - Meningeal thickening
  - Atrophy of the spinal cord; lower thoracic region in particular
  - Lateral funicular degeneration
- Microscopic:
  - Leptomeningeal and parenchymal infiltration of the spinal cord by lymphocytes and macrophages
  - Hyaline thickening of small blood vessels



Gross images of a spinal cord demonstrating atrophy of the lateral aspects



H&E and neurofilament immunostain demonstrating degeneration of the lateral aspects of the spinal cord
Picture courtesy: Dr. Steven Schwartz

- Intramyelinic vacuolization and demyelination in early stages → symmetric gliosis and degeneration involving long tracts
- Lateral columns tend to be most severely affected
- Anterior and, less commonly, the posterior columns may be affected
- Neurons are relatively well-preserved
- Adventitial fibrosis and scant perivascular inflammation have been seen in the cerebral white matter
- Cerebellar and brainstem involvement less common
- Sparse viral nucleic acids may be detectable within the spinal cord (In situ hybridization or polymerase chain reaction)

OTHER HIGH YIELD POINTS

- **First human retrovirus to be identified**
- Also causes adult T-cell leukemia
- Endemic in the Caribbean, South America, parts of Africa, southern Japan, and the Seychelles
- Transmitted by contact with infected bodily fluids
    - Sexual contact
    - Breastfeeding
    - Blood transfusion
- Age of onset is usually 25-60 years
- Progressive spastic paraparesis and sphincter disturbance
    - Most patients are chair-bound within 10 years
- Limited robust treatment options available

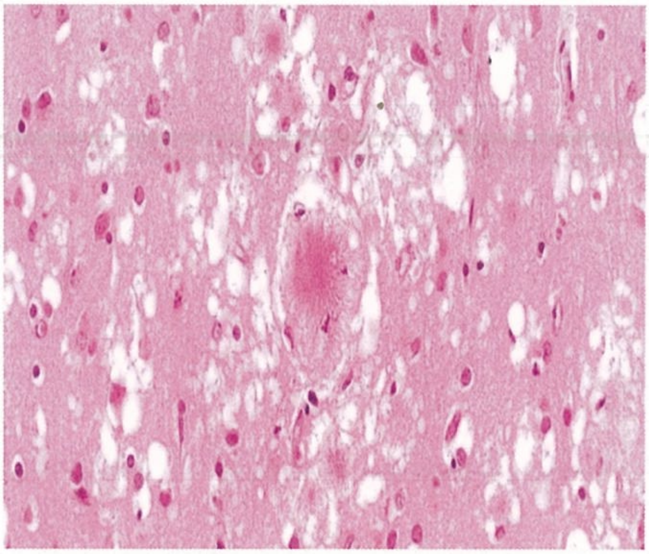
RUBELLA

MORPHOLOGY

- Macroscopic:
    - Rubella encephalitis
        - Usually consequence of first-trimester infection
        - Microcephaly, hydrocephalus, and foci of cavitation in the cerebral white matter
    - Progressive rubella panencephalitis
        - Cerebral atrophy
        - Cerebellum especially infected
- Microscopic:
    - Rubella encephalitis
        - Chronic lesions consisting of vascular and parenchymal mineralization are common
        - Basal ganglia and thalamus are particularly involved
        - May show findings of an active meningoencephalitis
    - Progressive rubella panencephalitis
        - Widespread neuronal and white matter destruction
        - Leptomeningeal and perivascular infiltration by lymphocytes and macrophages
        - Severe gliosis
        - Fibrinoid necrosis and mineralization of small blood vessels
        - No inclusion bodies are seen

OTHER HIGH YIELD POINTS

- Small enveloped RNA virus in the Togavirus family
- Causes German measles, a benign exanthematous disease, in children and adults
    - Complicated by arthritis in some cases
    - Rarely is complicated by a post-infectious ADEM
- Most cases of fetal infection are associated with symptomatic maternal infection during pregnancy
    - Approximately 35% of cases occur in subclinical maternal infection
- Risk of teratogenic fetal damage is approximately 50% during the first month of pregnancy
    - Declines to 5% by the fourth month
- Rarely seen in countries with vaccination programs; remains a health problem in developing countries
- Classic syndrome: cardiac and vascular malformations, cataracts, intellectual disability, microcephaly, and deafness
    - Occurs only after first-trimester infections
- Second-trimester infections usually limited to intellectual disability and deafness
- "Expanded" syndrome of continuing rubella infection may occur
- Includes pneumonitis and hepatosplenomegaly with severe thrombocytopenia
- Panencephalitis very rare complication
    - Manifests up to a decade or more following the initial infection
    - Intellectual disability, ataxia, seizures, spasticity, and choreoathetosis
    - Progresses slowly over several years
    - Patient ultimately becomes decerebrate, followed by death



PRION DISEASES

STEVEN N. SCHWARTZ, MD

5. PRION DISEASES

GENERAL CONSIDERATIONS

PRION DISEASES

MORPHOLOGY

- Gross findings are variable
    - Can be grossly normal
    - Can show variable atrophy in cerebral cortex, neostriatum, cerebellar cortex
    - Hippocampus generally grossly normal
- Extent of gross findings does not correlate with disease duration
- Pathology most prominent in cortical and deep gray matter
    - Neuronal loss
    - Astrocytosis
    - Microgliosis
    - **Spongiform change**
    - Deposition of PrP^{Sc}
    - In some cases, fibrillary PrP^{Sc} aggregates or amyloid plaques
- Neuropil vacuolization can also be seen focally in Alzheimer disease and Lewy body disease
    - Careful examination for Lewy bodies and neurofibrillary tangles should be performed to rule these out

OTHER HIGH YIELD POINTS

- Genetic forms of prion disease caused by mutations in **PRNP gene on chromosome 20**
- All forms are universally fatal
- Incubation period is years to decades
- Risk of transmission
    - Tissue should be handled carefully to avoid transmission
    - Equipment should ideally be incinerated
- CSF testing for 14-3-3 protein can aid in the diagnosis
    - Elevated in > 90% of sporadic CJD patients
    - Not disease-specific
    - Found in about 50% of variant CJD patients
- **RT-QuIC** is a newer test that can detect prion proteins in CSF
- PrP^{Sc} can be seen at low levels on immunoblotting assay of lymphoreticular tissue
- Immunohistochemistry for PrP following protease treatment is specific but not sensitive

MAIN POINTS FOR PRION DISEASES

	CJD	**Variant CJD**	**GSS Disease**	**Fatal Familial Insomnia**
Gross Findings	Variable	None (normal)	Variable	Variable
Histologic Findings	Global spongiform changes (especially sporadic form)	Florid amyloid plaques, protease-resistant PrP^{Sc}	Multicentric large plaques, protease-sensitive PrP^{Sc}	Thalamic gliosis
Clinical Features	Rapidly progressive dementia, average age 60 for sporadic and 40s-50s for familial	Psychiatric symptoms predominate, onset in 20s-30s	Variable presentation, prototypical presentation is ataxic form	Variable presentation, sleep-wake cycle alterations typical

PRION DISEASES

GERSTMANN-STRAUSSLER-SCHEINKER DISEASE

MORPHOLOGY

- Variable gross appearance
- **Multicentric large PrP amyloid plaques**
    - Sensitive to protease

OTHER HIGH YIELD POINTS

- Very rare: 2-5 cases per 100 million persons per year
- Associated with various mutations in PRNP gene
- Variable clinical presentation
- Prototypical presentation is ataxic form
    - Difficulty walking
    - Leg pains
    - Paresthesias
    - Dysarthria
    - Ocular dysmetria
    - Behavioral changes
- Lasts for months to several years

FATAL FAMILIAL INSOMNIA

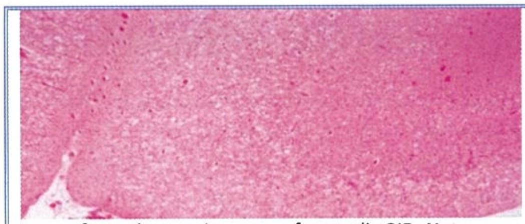
MORPHOLOGY

- Variable gross appearance
- Gliosis can be seen in thalamic nuclei

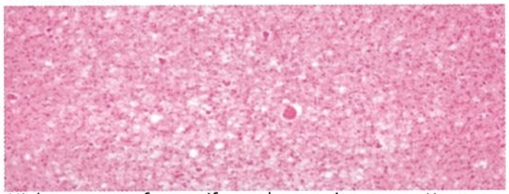
OTHER HIGH YIELD POINTS

- Missense mutation at codon 178 in PRNP gene
- Average onset 49 years
- Variable clinical presentation
    - Sleep-wake cycle alterations
    - Dysautonomia
    - Motor signs
    - Weight loss
    - Dementia
- Frequently elevated plasma catecholamine and cortisol

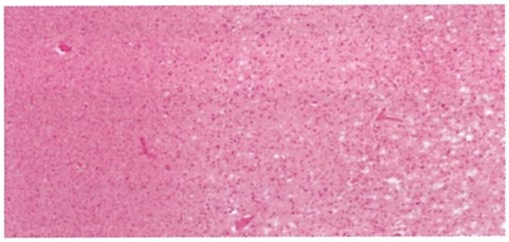
5. PRION DISEASES



Spongiform changes in a case of sporadic CJD. Note extensive involvement of gray matter with relative sparing white matter



Higher power of spongiform changes in gray matter



Higher power of interface between gray and white matter
Picture courtesy: Bartholomew White, MD

CREUTZFELDT-JAKOB DISEASE

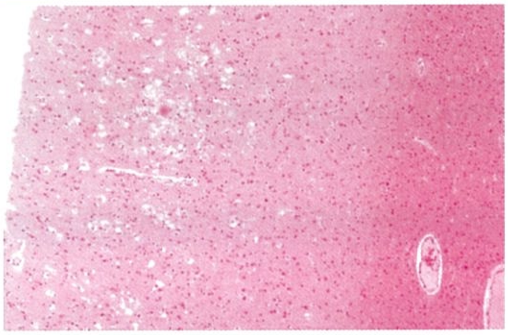
MORPHOLOGY

- Variable gross appearance
- Spongiform change generally prominent and ubiquitous in sporadic CJD

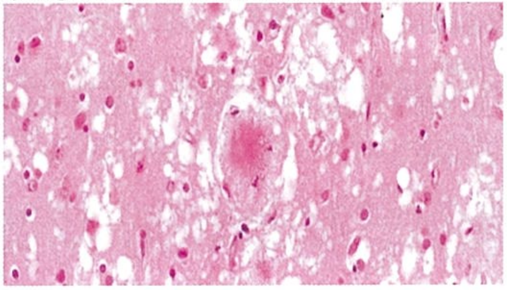
OTHER HIGH YIELD POINTS

- **Most common human prion disease**
  - > 85% of total cases
- Large majority sporadic
  - Incidence is 1 per 1 million persons per year
- Up to 10% of cases are familial
- Rare cases iatrogenic
- Mean age of symptom onset is 60 years for sporadic form
- Familial form presents earlier (40s-50s)
- Presents as rapidly progressive dementia
  - Myoclonus
  - Tremor
  - Ataxia
  - Rigidity
  - Seizures
  - Cortical blindness in a minority of cases
- Death usually occurs in fewer than 2 years (few months to 5 years)

Path Presenter   Path Presenter   Path Presenter   Path Presenter



Variant CJD. Note the spongiform changes with relative sparing of white matter and florid amyloid plaques



Higher power of amyloid plaque
Picture courtesy: Robert Schmidt, MD

VARIANT CREUTZFELDT-JAKOB DISEASE

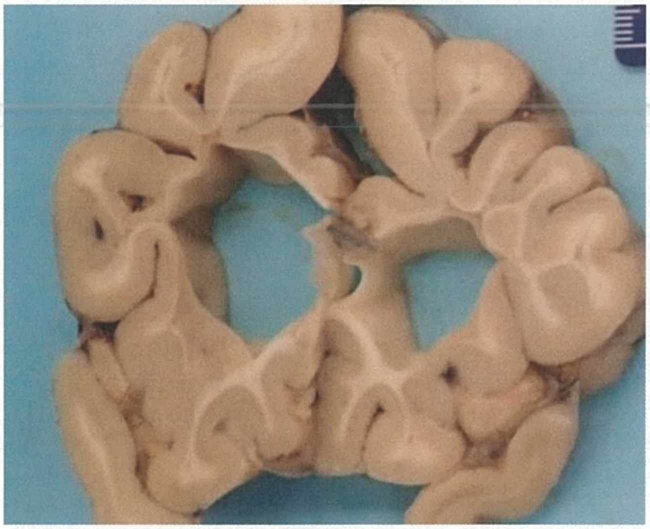
MORPHOLOGY

- Grossly appears normal
- **Florid amyloid plaques**
  - Large plaques surrounded by spongiform vacuoles
- Abundant deposition of protease-resistant PrP^{Sc} in neuropil
  - Only type of prion disease that can be distinguished with histology alone

OTHER HIGH YIELD POINTS

- Earlier onset than other forms of CJD (20s-30s)
- Presents with predominantly psychiatric symptoms
  - Depression
  - Schizophrenia-like psychosis
  - Behavioral changes
  - Paresthesias
  - Ataxia
  - Involuntary movements
- Death usually occurs in 13-14 months
- Symmetric high FLAIR signals in pulvinar on imaging in > 90% of cases

Path Presenter   Path Presenter



DEMYELINATING AND DYSMYELINATING DISEASES

RAQUEL T. YOKODA, MD

6. DEMYELINATING AND DYSMYELINATING DISEASES

DEMYELINATING AND DYSMYELINATING DISEASES

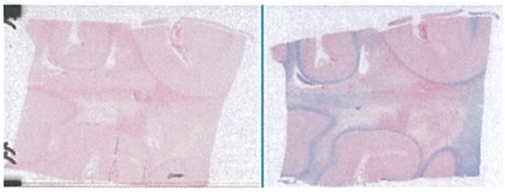
MULTIPLE SCLEROSIS AND VARIANTS

MORPHOLOGY

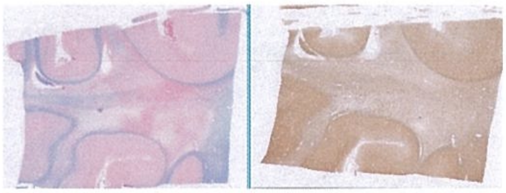
- Gross findings are variable
- Gross: well-circumscribed area of white matter pallor
- Marked myelin loss with relative axonal preservation
- Plaques may have different stages in the same patient
- Active vs. inactive; acute vs. chronic
- **Active plaque:** Preferential loss of myelin in comparison to axons; prominent lymphocytic perivascular cuffs, predominantly T-lymphocytes over B-lymphocytes; a large number of macrophages, reactive gliosis, cerebral edema; axonopathy, focally swollen axons (axonal spheroids) usually to the edge of the plaque
- **Inactive plaques:** Quiescent, nearly complete loss of myelin; oligodendroglia are absent from the center of the plaque; only naked axons, relative preservation, but axonal loss is present
- **Tumefactive MS**: Large, unifocal, contrast-enhancing cerebral hemispheric mass, can be mistaken for a neoplasm
- **Balo concentric sclerosis:** Extremely rare, monophasic form of MS with concentric rings of preserved and absent myelin; patterns could be related to oxidative damage

OTHER HIGH YIELD POINTS

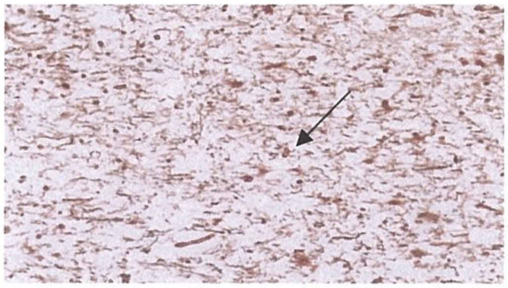
- Demyelinating: Loss or damage to the myelin
- Dysmyelinating: Improper formation or maintenance of myelin (often genetic or congenital)
- Multiple sclerosis is the most common demyelinating disease of the CNS
- Reflects genetic, autoimmune, and environmental processes
- Variable symptoms depending on location of the demyelinating plaques
- Usually young patients 20-40 years old
- Female predominance 2:1
- 80% of cases → relapsing and remitting disease (RRMS)
- RRMS may evolve to secondary progressive form (SPMS) with no remitting
- Acute tumefactive form of MS has distinctive C-shaped/horseshoe lesions with partial rim enhancement on radiology
- MR spectroscopy → elevated choline
- Differential diagnosis: Neoplasia, PML



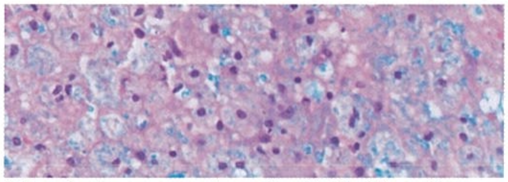
H&E and LFB showing white matter pallor, myelin loss (demyelinating lesion) with U-fiber sparing



The LFB and NF showing relative preservation of axons



NF stain high power shows spheroid bodies (arrow)



LFB stain shows macrophages "stuffed" with myelin

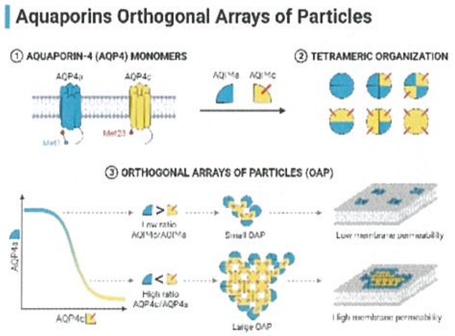
NEUROMYELITIS OPTICA (NMO, DEVIC DISEASE)

MORPHOLOGY

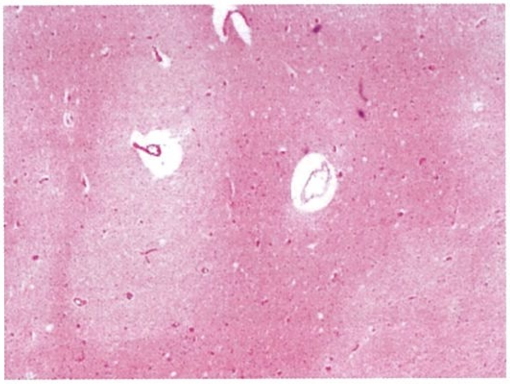
- Myelinopathy can be necrotizing in the optic nerve, and longitudinally extensive myelitis involves many vertebral bodies
- Lesions may involve basal ganglia, hypothalamus, area postrema, cerebellum (NMO spectrum disorder, abbreviated NMO-SD)

OTHER HIGH YIELD POINTS

- **Female to male 9:1**
- Simultaneous optic neuritis and transverse myelitis
- Differential diagnosis: RRMS, paraneoplastic or infectious transverse myelinitis, neurosarcoidosis, myelopathy in systemic lupus erythematosus, infarction of the spinal cord, neoplasia
- **Serologic test available**: Detect the NMO-IgG antibody against aquaporin-4
- The immune attack is against AQP4 (astrocytic water channel aquaporin-4)
- **Anti-AQP4 IgG** binds to the astrocytic processes (glia limitans and Virchow-Robin spaces) → demyelination as a bystander effect


Aquaporins Orthogonal Arrays of Particles
① AQUAPORIN-4 (AQP4) MONOMERS
AQP4a
AQP4c
Met1
Met23
② TETRAMERIC ORGANIZATION
③ ORTHOGONAL ARRAYS OF PARTICLES (OAP)
AQP4a
AQP4c
Low ratio
Small OAP
Low membrane permeability
High ratio
AQP4c/AQP4a
Large OAP
High membrane permeability

AQP4 antibodies will disrupt the water balance of the cell membrane and promote a demyelination process similar to central pontine myelinolysis, except that it will affect areas rich in AQP4 (optic tract, spinal cord)
Created with BioRender



H&E showing punctate foci of demyelination typically around small veins and venules, perivenular encephalomyelitis
Picture courtesy: Timothy Richardson, DO, PhD

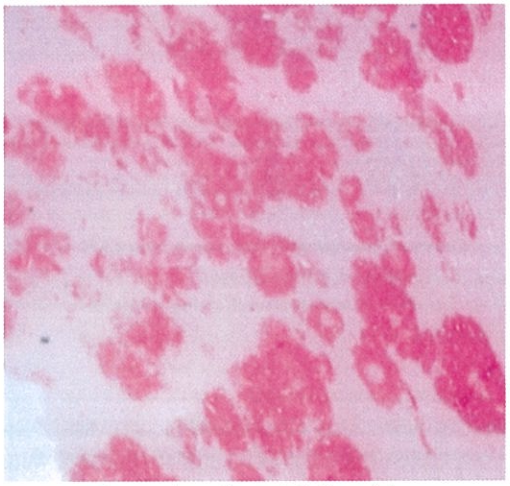
ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

MORPHOLOGY

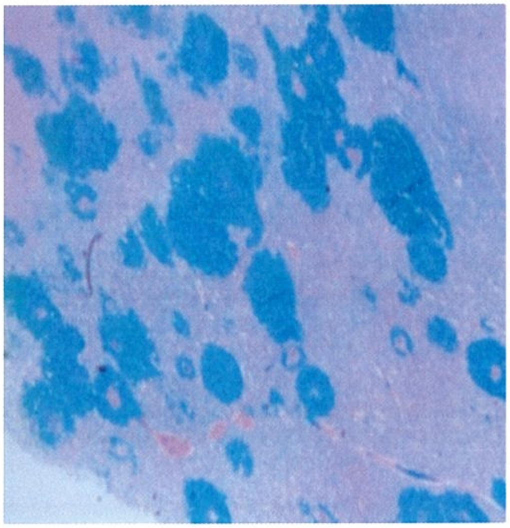
- Typically monophasic inflammatory/autoimmune demyelinating lesions on the CNS white matter after an inciting event (post-infectious or following vaccination)
- Perivenular distribution of the demyelination

OTHER HIGH YIELD POINTS

- The first reported cases in the 1920s → children's and young adults' response to smallpox vaccination
- **Predilection for children**
  - ➢ Inciting event can be days or weeks prior (measles, mumps, varicella, rubella infection; smallpox or rabies vaccinations; bacterial infections with *Mycoplasma pneumoniae* or *Campylobacter jejuni*)
- Differential diagnosis: MS



H&E shows hemorrhagic lesion in balls and rings
Picture courtesy: Timothy Richardson, DO, PhD



LFB shows loss of myelin in the background of hemorrhagic angiitis
Picture courtesy: Timothy Richardson, DO, PhD

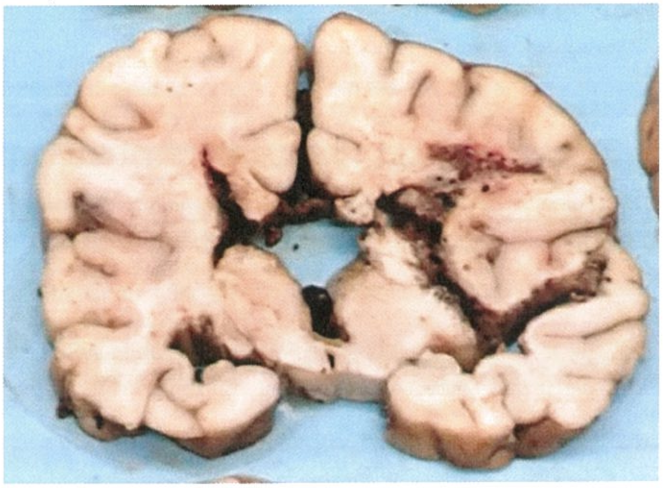
ACUTE HEMORRHAGIC LEUKOENCEPHALITIS (AHLE, WESTON-HURST SYNDROME)

MORPHOLOGY

- Destructive process; perivascular distribution with vascular necrosis
- Can have superimposed white matter ischemic lesions
- Involves subcortical and deep white matter, some cases with spinal cord involvement
- Gross: Marked edema, congestion, and petechial hemorrhages in the white matter; may involve brainstem, cerebellum, spinal cord
- Microscopy: Similar to ADEM but with superimposed venous angiitis, fibrin leakage, axonopathy with axonal spheroids, and microinfarction

OTHER HIGH YIELD POINTS

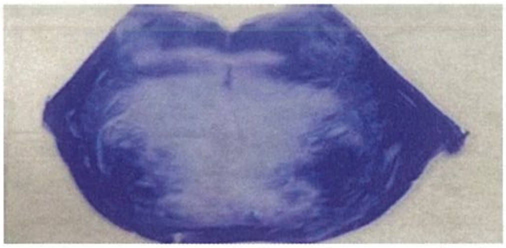
- Mortality rate is very high despite immunosuppressants and plasmapheresis
- **All ages susceptible**
- Related to an episode of upper respiratory tract infection within 2 weeks of CNS symptom onset
- **Abrupt onset** of fever, stiff neck, hemiplegia, impaired consciousness, seizures, and other focal signs
- Differential diagnosis: Fat embolism, thrombotic thrombocytopenic purpura, disseminated intravascular coagulopathy, arsenical treatment for parasitic diseases, malaria



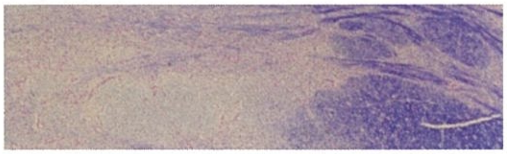
Gross appearance in an autopsy case of AHLE

6. DEMYELINATING AND DYSMYELINATING DISEASES

CENTRAL PONTINE MYELINOLYSIS (CPM)



Low-power view (LFB stain) of central pontine myelinolysis
Picture courtesy: Timothy Richardson, DO, PhD



LFB shows areas with complete loss of myelin
Picture courtesy: Timothy Richardson, DO, PhD

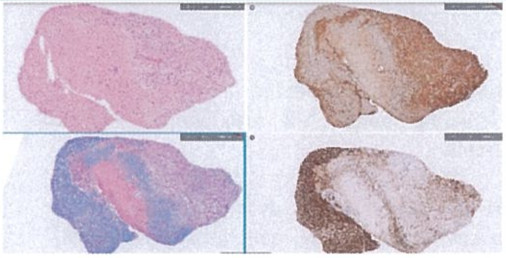
MORPHOLOGY

- Osmotic demyelination syndrome (edema, myelinolysis)

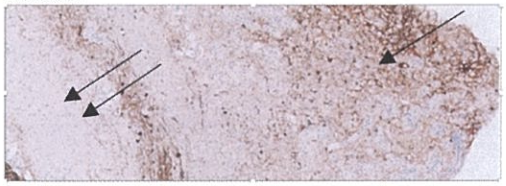
OTHER HIGH YIELD POINTS

- Complication of rapid treatment of marked hyponatremia
- Occurs often in the setting of alcohol use disorder (40% cases)
- Other associated predisposing conditions: Hepatic dysfunction, malnutrition
- Most common site: Central pons
- Extrapontine sites: LGN, cerebellum
  - ➢ Clinical: Abrupt encephalopathy following correction of hyponatremia
  - ➢ Locked-in syndrome, dysarthria, dysphagia, quadriparesis
- Differential diagnosis: Other causes of demyelination
- Prognosis is variable, some patients can fully recover while others will have different levels of permanent neurologic sequelae

MARCHIAFAVA-BIGNAMI DISEASE (MBD)



H&E and CD163 on top, followed by LFB and NF below showing active demyelinating lesion of the corpus callosum



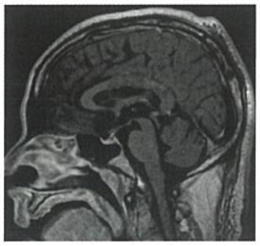
A closer look at the NF stain shows areas of relative preservation (single arrow) and areas of necrosis with complete loss of axons (double arrows)

MORPHOLOGY

- Gross: Affects the corpus callosum in patients with history of chronic alcohol abuse disorder, malnutrition, thiamine deficiency
- The lesion can show demyelination and necrosis followed by atrophy
- **Myelin degeneration and necrosis**

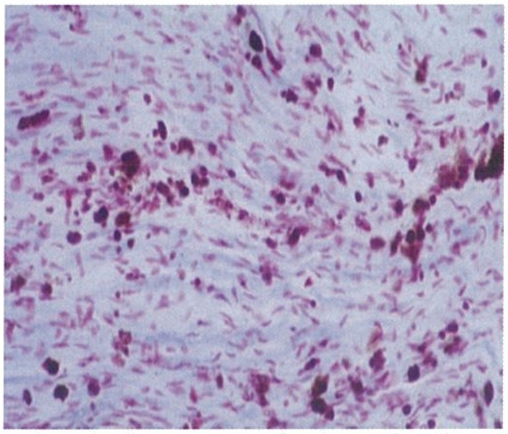
OTHER HIGH YIELD POINTS

- Rare; symptoms may vary from dysarthria to seizures, paranoia, dementia
- Levels of demyelination and necrosis are variable, NF stain may show partial preservation and areas of total loss of axons
- Clinical history and radiology are key for the diagnosis



T1-weighted, post-contrast MRI brain of a patient with MBD

METACHROMATIC LEUKODYSTROPHY



Acid cresyl violet stain in a peripheral nerve shows brown metachromasia characteristic of sulfatide deposits
Open-source image: [Lysosomal storage diseases (neuropathology-web.org)]

MORPHOLOGY

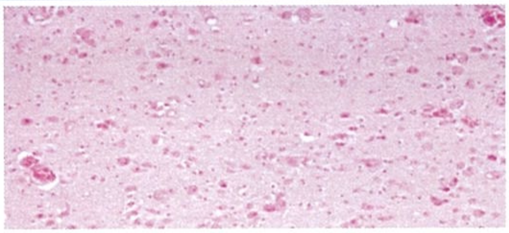
- On H&E, sulfatides deposits are pink; become brown in acid cresyl violet (brown metachromasia)

OTHER HIGH YIELD POINTS

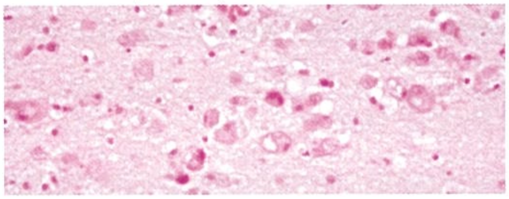
- Autosomal recessive lysosomal disorder → deficiency of arylsulfatase A → buildup on sulfatides → myelin destruction (dysmyelinating disease)
- **Progressive lysosomal storage disease (LSD)**; lysosomal storage of sulfatides kills oligodendrocytes and Schwann cells
- Hypotonia, weakness, spasticity, progressive peripheral neuropathy, blindness, psychomotor delay
- Onset: Late infantile < 4 years; early juvenile 4-6; late juvenile 6-16; adult > 16
- Differential diagnosis: Krabbe disease, X-linked adrenoleukodystrophy, Cavanan disease

6. DEMYELINATING AND DYSMYELINATING DISEASES

GLOBOID CELL LEUKODYSTROPHY (KRABBE DISEASE)



H&E low magnification shows globoid cells
Picture courtesy: Timothy Richardson, DO, PhD



H&E Krabbe disease, globoid cells, and myelin pallor
Picture courtesy: Timothy Richardson, DO, PhD

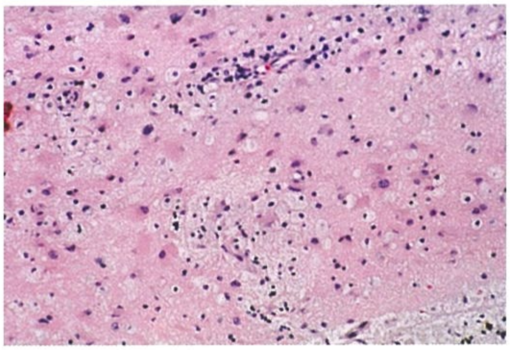
MORPHOLOGY

- White matter is devoid of oligodendrocytes, dysmyelinating disease
- Peripheral nerves show demyelinative axonal neuropathy with accumulation of galactocerebroside in Schwann cells and macrophages
- Neuronal loss is seen in the thalamus, brainstem and cerebellum
- No other organs are affected

OTHER HIGH YIELD POINTS

- 30% of myelin lipids are galactosylceramide (galactocerebroside) and its sulfated variant sulfatide
- **Deficiency of GALC causes Krabbe disease**
- Children affected are normal at birth, then develop spasticity, progressive neurologic regression, seizures, peripheral neuropathy, blindness, myoclonus
- Usually, death occurs in 2-3 years, many in a few months
- Accumulation of the related metabolite galactosylsphingosine (psychosine) is toxic to oligodendrocytes
- Toxicity and lipid imbalance → severe myelin degeneration
- EM: Macrophages with tubular inclusions

ADRENOLEUKODYSTROPHY (ALD)



H&E in ALD shows gliosis and inflammation
Open-source image: Peroxisomal diseases (neuropathology-web.org)

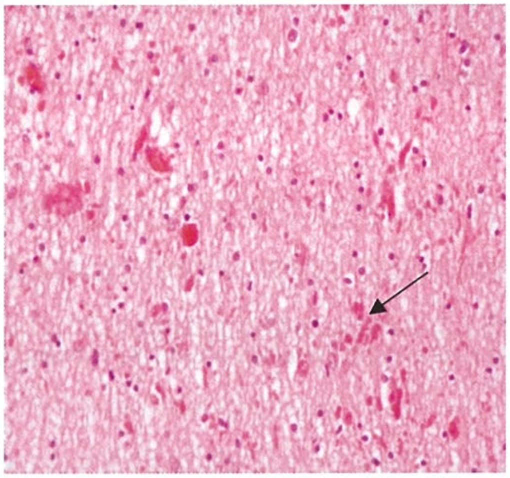
MORPHOLOGY

- Gross: White matter of parieto-occipital lobes affected
- Histology similar to other leukodystrophies but with lymphocytic cuffs, predominantly CD8-positive T-cells

OTHER HIGH YIELD POINTS

- X-linked **gene defect in ABCD1 transporter (Xq28)**; dysmyelinating
- Defective peroxisomal beta oxidation of very long chain fatty acids (VLCFA)
- VLCFA in myelin induces myelin instability → immune-mediated process involving lipid antigen presentation and substantial myelin destruction
- Variable adrenal dysfunction
- Variant adrenomyeloneuropathy → progressive paraparesis
- EM: Cleft-like trilamellar inclusions containing VLCFA can be seen in Schwann cells and macrophages; swollen adrenal cortical cells

ALEXANDER DISEASE



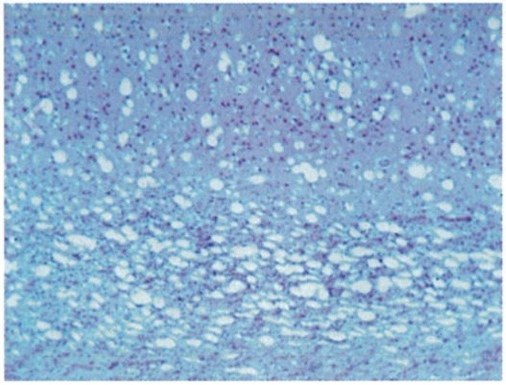
H&E at 20x shows the dysmyelinating disease with abundant Rosenthal fibers (arrow)
Picture courtesy: Timothy Richardson, DO, PhD

MORPHOLOGY

- Gelatinous, granular gray, or yellow white matter
- Microscopy: Rosenthal fibers (subpial, periventricular, perivascular), prominent and progressive frontal to occipital loss of white matter, may have cystic degeneration
- Variable white matter pallor with abundant deposition of Rosenthal fibers
- Affects cerebellar white matter, dentate nucleus, brainstem nuclei, optic nerves, spinal cord
  - ➢ GFAP, alpha B crystallin, heat shock proteins

OTHER HIGH YIELD POINTS

- Dysmyelinating disease → rare leukodystrophy
- Dominant, gain-of-function mutation in **GFAP gene 17q21** leads to abnormal metabolism in astrocytes (proteasome dysfunction)
- Variants: Infantile 2-4 years old; juvenile 4-12 years; adult > 12 years
- Presentation: Progressive cognitive/motor symptoms, ataxia, bulbar/pseudobulbar dysfunction, megalencephaly, seizures (adult onset has rare seizures and no megalencephaly)
- Median survival: Infantile 14 years; juvenile and adult 25 years
- Differential diagnosis: Other leukoencephalopathies, other Rosenthal fiber-rich lesions, toxic or metabolic disorders



H&E shows spongy degeneration
Open-source image: Leukodystrophies (neuropathology-web.org)

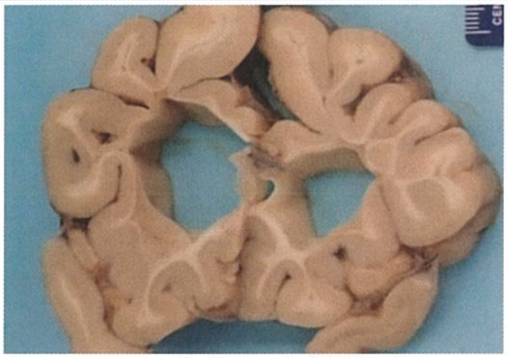
CANAVAN DISEASE

MORPHOLOGY

- Multiple vacuoles in deeper cortical layers, cortex-white matter junction, white matter, and cerebellum; spongy degeneration, no myelin in advanced stages
- No fibrous gliosis, but Alzheimer type II astrocytes can be seen
- As disease progresses, brain weight is reduced and white matter atrophy develops

OTHER HIGH YIELD POINTS

- Autosomal recessive, ASPA gene, encodes aspartoacylase (17pter-p13)
- First few months of life with macrocephaly, lack of head control; later, hypotonia followed by spasticity, blindness, seizures, irritability
- Usually, death occurs when patients reach their teens
- Increased N-acetylaspartic acid in the urine, CSF, and plasma
- EM: Intramyelinic vacuolation
- Deficiency of aspartoacylase → build up substrate N-acetyl-L-aspartate (NAA)
- Diagnosis can be made by measuring NAA levels in blood, urine, CSF



Gross appearance of leukoencephalopathy with vanishing white matter

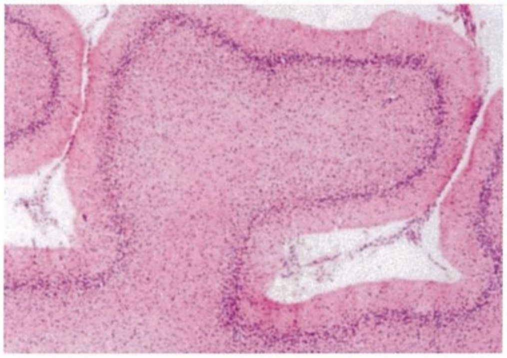
LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER (VWM, CHILDHOOD ATAXIA WITH CENTRAL HYPOMYELINATION)

MORPHOLOGY

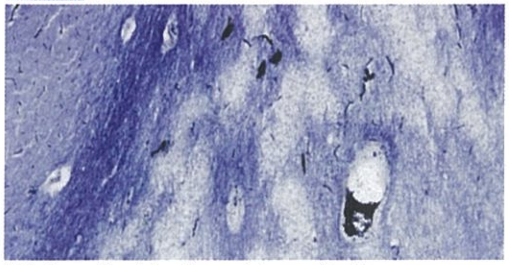
- White matter is extremely rarefied; cortex and gray matter structures are spared

OTHER HIGH YIELD POINTS

- Ataxia, spasticity, and less frequently cognitive deterioration
- Slowly progressive, fatal
- Episodes of neurologic deterioration triggered by fever, illness, head trauma
- Affects children, but older individuals can be affected with milder symptoms
- Mutations of genes encoding any of the 5 subunits of the eukaryotic translation initiation factor 2B (elF2B, EIF2B1-EIF2B5, elF2B epsilon)



H&E shows cerebellar degeneration
Open-source image: Leukodystrophies (neuropathology-web.org)



LFB shows tigroid pattern of dysmyelination

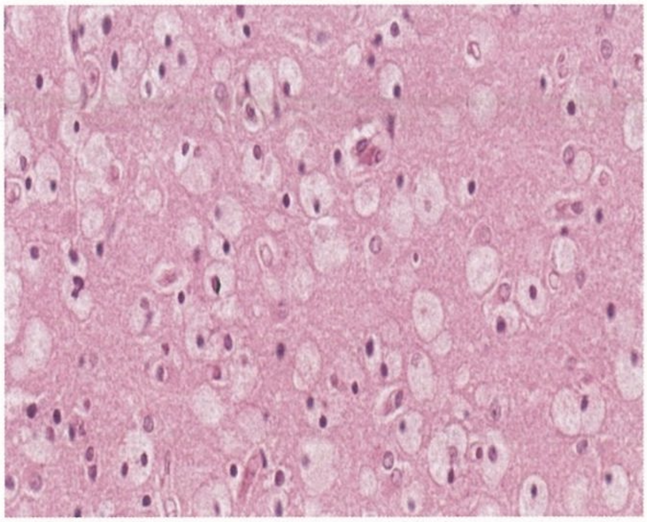
PELIZAEUS-MERZBACHER DISEASE

MORPHOLOGY

- Loss of myelin spares the subcortical fibers, **tigroid pattern of myelin loss**

OTHER HIGH YIELD POINTS

- Rare, X-linked; female carriers are mostly normal; some carriers with point mutations show mild symptoms
- Abnormal myelin protein: Proteolipid protein 1 (PLP1) and spliced isoform DM20 caused by mutation of the PLP1 gene on Xq22
- Wide clinical spectrum
- Presents in the first year of life with delay in motor development
- Reduced white matter volume and increased signal intensity in FLAIR MRI
- There is no peripheral neuropathy
- An autosomal recessive variant called Pelizaeus-Merzbacher-like disease (PMLD) → caused by mutations on the GJC2 gene that disrupts SOX10 activity

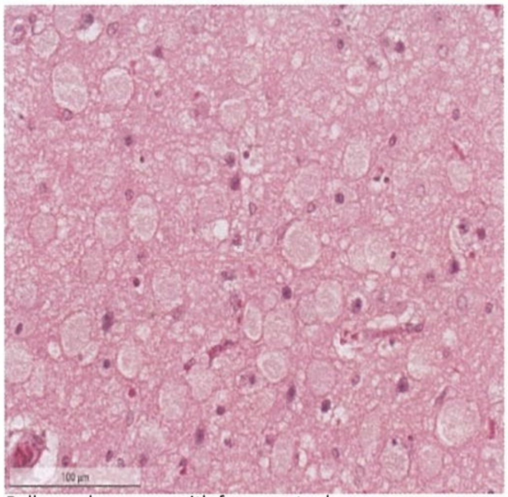


INHERITED AND ACQUIRED METABOLIC DISEASES

LAKSHMI RAMACHANDRAN NAIR, MD

7. INHERITED AND ACQUIRED METABOLIC DISEASES

INHERITED AND ACQUIRED METABOLIC DISEASES



Ballooned neurons with foamy cytoplasm

TAY-SACHS DISEASE (INFANTILE GM2 GANGLIOSIDOSIS)

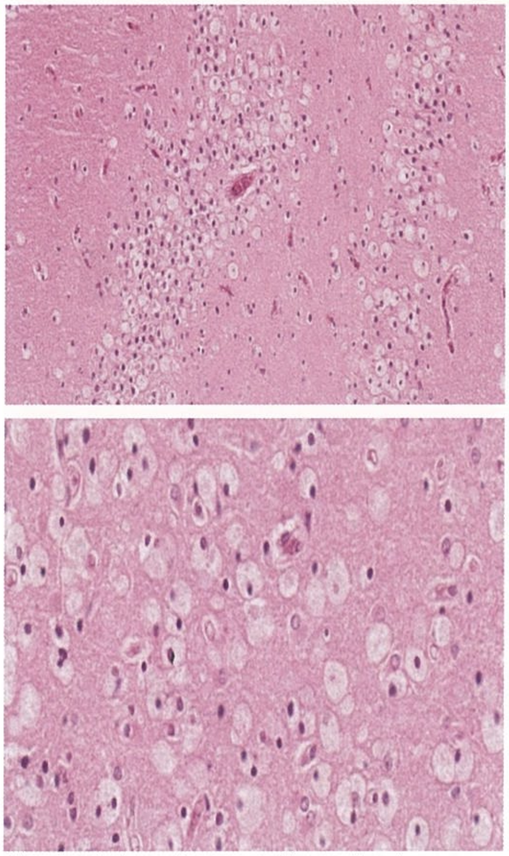
MORPHOLOGY

- Gross: White matter loss and atrophy of gyri
- Microscopy: **Ballooned neurons with foamy cytoplasm** are seen in CNS and PNS
  - ➢ Positive for LFB and Sudan black
  - ➢ PAS negative in paraffin blocks, positive on frozen section slides

OTHER HIGH YIELD POINTS

- **Autosomal recessive**
- **Lack of hexosaminidase A or B**, or lack of their activator protein
- **Increased ganglioside deposition**, which is soluble, hence negative for PAS on paraffin sections
- More severe than juvenile and adult variants of gangliosidosis
- Progressive retardation, muscle tone problems, and visual disturbances
- Other organs are also involved

Path Presenter



Abundant ballooned neurons with cytoplasmic storage material

Path Presenter

NIEMANN-PICK DISEASE

MORPHOLOGY

- Gross: Varying degrees of cerebral atrophy and gliosis with firm white matter are seen in all types with nervous system involvement
- Microscopy:
  - ➢ Type A
    - ▪ Ballooned neurons and glial cells
    - ▪ Gliosis and demyelination can be seen in white matter
    - ▪ Foamy "Niemann-Pick" cells are seen systemically, in bone marrow, spleen, lymph nodes, and alveolar spaces
    - ▪ Lymphocytes can show small, discrete vacuoles
  - ➢ Types C and D
    - ▪ Ballooned neurons with preferential predominance in basal ganglia, brainstem, and spinal cord
    - ▪ Tau immunopositive neurofibrillary tangles and neuroaxonal dystrophy can also be seen
- PAS-positive cells with granular storage material can be appreciated on frozen section slides in all types with nervous system involvement
- Ultrastructurally, the neuronal storage material is seen as membrane-bound cytoplasmic bodies

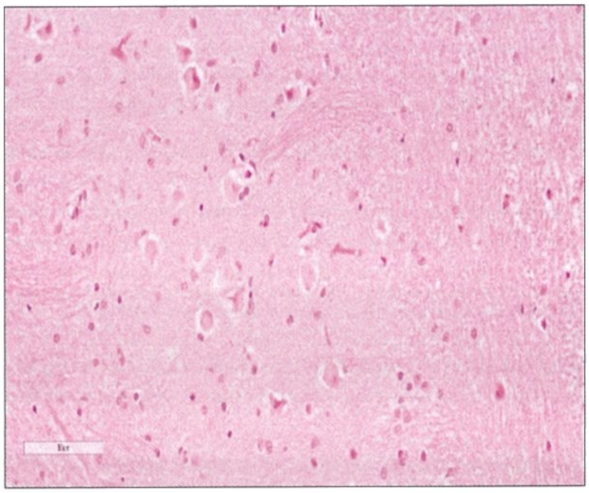
OTHER HIGH YIELD POINTS

- Autosomal recessive
- Group I (sphingomyelinase deficiency via chromosome 11p) and Group II (defective cholesterol esterification via chromosome 18q)
- Group I (Type A) and Group II (Types C and D) can involve nervous system
- Type A is detected in infancy with hepatosplenomegaly and failure to thrive
  - ➢ Survivors develop epilepsy, spasticity, and memory problems
- Type B is a non-neuropathic visceral form, mostly a benign disease in young adults
- Type C presentation can range from neonatal failure to thrive to eye movement disorders and psychotic symptoms in adulthood

NEURONAL CEROID LIPOFUSCINOSES (BATTEN DISEASE, CLN)

MORPHOLOGY

- Gross: Brain atrophy is seen in all types, but to varying extents
  - Most severe in infantile form with shrunken cortex and rubbery white matter
  - Minimal atrophy is seen in adult type, usually limited to frontal and cerebellar regions
- Microscopy: Widespread presence of storage material
  - Tinctorial differences can be seen among different types
  - Loss of neurons with subsequent dense astrocytosis, increase in macrophages, and myelin loss
  - Intracellular lipopigment and storage material (positive for PAS and LFB) can be seen in many cell types, especially neurons
  - Neuronal loss and demyelination are more prominent in infantile and juvenile forms
  - Adult type shows less severe histopathologic changes
  - Juvenile type shows vacuolated lymphocytes in peripheral smear
  - Ultrastructural studies show storage material as "granular osmiophilic deposits" (GROD) in infantile type
  - Late infantile type shows "curvilinear bodies" (CV) and juvenile type (gastrointestinal neurons) shows "fingerprint bodies"
  - CNS neurons in juvenile type show a mixture of both curvilinear and fingerprint bodies
  - All combinations are reported in adult-type CLN

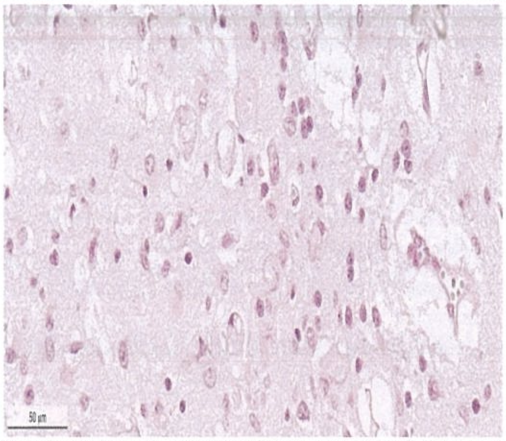


Intracellular lipopigment deposition in neurons

OTHER HIGH YIELD POINTS

- A group of many subtypes: CLN1-CLN14, all autosomal recessive except some CLN4 forms
- CLN1, infantile type: Rapidly progressive irritability, hypotonia, and retardation in the initial year
  - Flat EEG by 3 years and usually death in 3-10 years
- CLN2, late infancy type: Onset with seizures around 1.5 to 4 years
  - Spasticity, visual problems, worsening epilepsy, and death by 4-10 years
- CLN3, juvenile type: Onset with visual problems around 4-9 years
  - Further disease progression with epilepsy, dementia, and dysarthria
  - Death usually occurs by 15-30 years of age
- CLN4, adult type A or B: Onset around 30 years
  - Type A: Progressive myoclonic epilepsy is the most prominent symptom
    - Dysarthria, dementia, and ataxia can be seen
  - Type B: Can have tics and facial dyskinesias
    - May survive for many years
- CLN5, Finnish variant late infancy type: Onset around 4-7 years
  - Motor clumsiness is the initial presentation, followed by visual problems, epilepsy, ataxia, and cerebellar signs
  - Death usually by the early 20s
- CLN6, variant late infantile/early juvenile type: Similar clinical picture to CLN5 but with a wider age range
- Remaining subtypes are relatively rare
- Storage material is lipopigment containing subunit c of mitochondrial ATP synthase (SCMAS) in most types, with additional sphingolipid activator proteins (SAPs) A and D in CLN8
  - CLN1 has only SAPs A and D
  - Both storage materials are insoluble and demonstrable in both
  - Paraffin and frozen sections

Path Presenter



Gaucher cells with crumpled "tissue paper-like" cytoplasm

Path Presenter

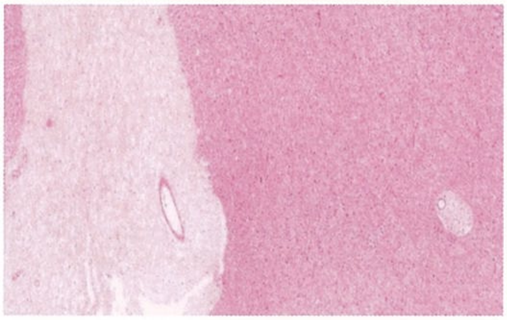
GAUCHER DISEASE

MORPHOLOGY

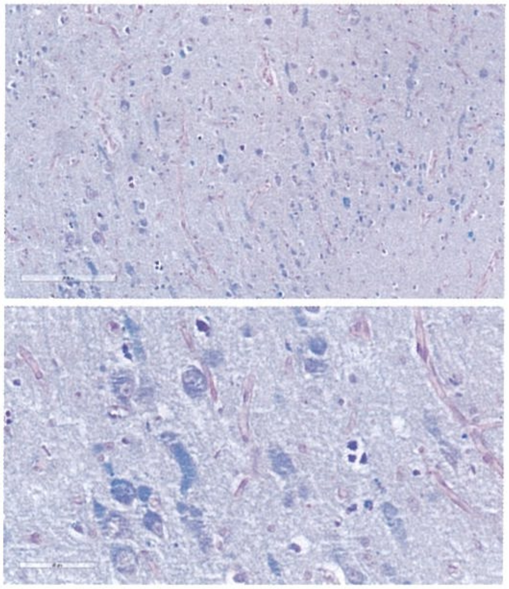
- Gross: Most cases have no apparent findings
- Microscopic:
  - Neuron dropout in superficial and deep gray matter, mainly in cranial nerve nuclei
  - Demyelination and gliosis in white matter
  - Large, PAS-positive "Gaucher cells" with crumpled tissue paper-like cytoplasm are seen in many areas of the nervous system, mainly in hippocampus, thalamus, and pons that can show perivascular affinity

OTHER HIGH YIELD POINTS

- Autosomal recessive (Types 2 and 3 involve the nervous system)
- Deficiency of **glucocerebrosidase** (GBA gene on 1q), which results in the accumulation of tissue glucocerebroside
- Type 2: Presents as hepatosplenomegaly and failure to thrive in infancy with developmental delay, cranial nerve involvement, and usually death in 1-2 years
- Type 3: Manifests around 5 years
  - Hypersplenism, epilepsy, mental retardation, and fractures
  - Risk factor for Lewy body disease and Parkinson disease



Enlarged perivascular spaces with macrophages



LFB-PAS staining showing distended neurons with LFB-positive material within the cytoplasm

MUCOPOLYSACCHARIDOSES

MORPHOLOGY

- Gross:
  - Widening of the skull, brain atrophy, and thickening of meninges can be seen
  - Dilated perivascular spaces can be appreciated as slits in advanced stages
- Microscopy:
  - Mucopolysaccharides are extremely water-soluble, hence not demonstrable in fixed tissues
  - Neuronal storage of mucopolysaccharides cannot be appreciated
    - Can be seen on frozen sections from other tissue types such as hepatocytes, endothelial cells, cartilage, fibroblasts, etc.
  - **Dilated perivascular zone with foamy macrophages** is the predominant histologic finding in the CNS
  - Neuronal storage of gangliosides can be demonstrated as **granular inclusions** positive for PAS, LFB, and Sudan black
- Ultrastructural examination shows storage material in stacks/ **"zebra bodies"**

OTHER HIGH YIELD POINTS

- Group of disorders with deficiency of glycosaminoglycan-cleaving enzymes leading to accumulation of mucopolysaccharides in lysosomes
- Occasionally, ganglioside deposition in neurons also can be demonstrated
- Closely resemble gangliosidosis
- Main types with CNS involvement are:
  - Hurler syndrome (Type IH mucopolysaccharidosis): Growth retardation, cloudy cornea, hepatosplenomegaly, and facial and skeletal abnormalities
  - Hunter syndrome (Type II mucopolysaccharidosis): Similar to the previous type but without corneal involvement
  - Sanfilippo disease (Type IIIA mucopolysaccharidosis): Developmental delay, behavioral problems, diarrhea, and frequent infections
- All are autosomal recessive except for Hunter syndrome (X-linked recessive)

Path Presenter

7. INHERITED AND ACQUIRED METABOLIC DISEASES

FABRY DISEASE

MORPHOLOGY

- Gross: Macroscopically unremarkable
- Microscopic: Intracytoplasmic storage material is seen in neurons, astrocytes, endothelial cells, and perivascular smooth muscle
  - ➢ Affects hippocampus, amygdala, entorhinal cortex, hypothalamus, brainstem nuclei, and spinal cord
  - ➢ Storage material is positive for PAS and birefringent with a Maltese cross appearance
  - ➢ Infarcts secondary to vasculopathy can be seen

OTHER HIGH YIELD POINTS

- Rare X-linked disorder with deficiency of **alpha-galactosidase A**, resulting in accumulation of intracellular glycosphingolipids
- Presents with angiokeratomas on skin and mucosa in childhood, ocular pathologies, and eventually leading to renal failure, cardiac failure, or stroke secondary to vasculopathy

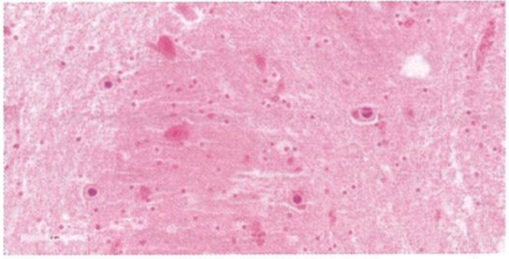
FARBER LIPOGRANULOMATOSIS

MORPHOLOGY

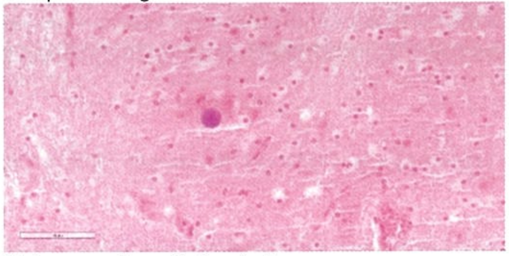
- Gross: Macroscopically unremarkable
- Microscopic: Neuronal storage of PAS-positive, birefringent material
  - ➢ Best appreciated in basal ganglia, brainstem, and anterior horns
  - ➢ Neuronal loss and gliosis are present
- Subcutaneous nodules show lipid-filled macrophages and associated granulomatous reactions
- Ultrastructural examination shows the presence of occasional zebra bodies in neurons
- Small, curvilinear, tubular bodies called "Farber bodies/banana bodies" can be seen in neurons and endothelial cells

OTHER HIGH YIELD POINTS

- Autosomal recessive disease with deficiency **of N-acylsphingosine amidohydrolase** (ASAH) on chromosome 8p, leading to increased ceramide levels
- Presents in infancy with retardation and feeding and breathing problems
- Subcutaneous and periarticular nodules are seen, resulting in painful and swollen joints



Low-power image of Lafora bodies in the dentate nucleus



High-power view of Lafora body

Picture courtesy: Dr. Robert Schmidt

LAFORA BODY DISEASE

MORPHOLOGY

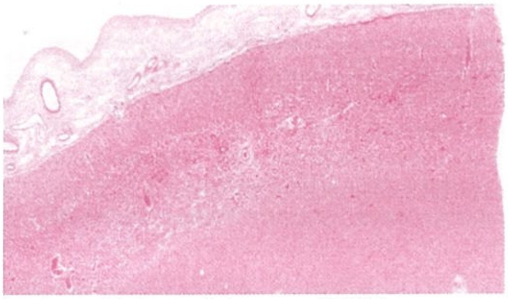
- Gross: Macroscopically unremarkable
- Microscopy: Many Lafora bodies in the cytoplasm of neurons and astrocytes
  - ➢ Round, deeply eosinophilic structures similar to corpora amylacea
  - ➢ PAS positive and metachromatic with crystal violet staining
  - ➢ Usually seen in the cerebral cortex, cerebellar cortex, and deep gray nuclei
  - ➢ Neuronal loss and gliosis can be seen, mostly in the dentate nucleus

OTHER HIGH YIELD POINTS

- Autosomal recessive inheritance
  - ➢ Mutation in either **laforin** gene (chromosome 6q) or **malin** gene (chromosome 6p)
  - ➢ Both result in defective carbohydrate metabolism and increased accumulation of polyglucosan bodies (Lafora bodies)
- Onset around 15 years with progressive neurodegeneration, dementia, and myoclonic epilepsy

Path Presenter

MITOCHONDRIAL ENCEPHALOMYOPATHIES



Laminar cortical necrosis in a case of MELAS

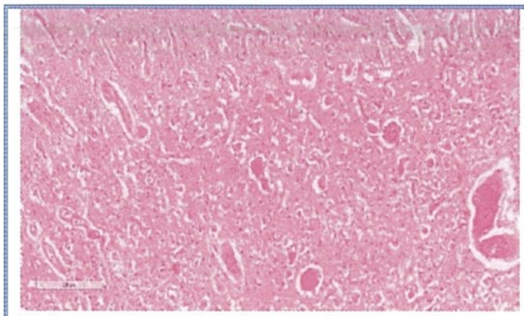
MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES (MELAS)

MORPHOLOGY

- Gross: Infarct-like cavitation and necrosis in the cerebral cortex, usually occipital cortex
  - ➢ Randomly scattered, do not follow a vascular distribution
- Microscopy: Infarct-like necrosis with surrounding vascular proliferation
  - ➢ Crests of gyri are more involved
  - ➢ Mineralization and fibrosis of blood vessel walls can be seen
- Skeletal muscle shows "ragged red" fibers with abnormal mitochondrial accumulation in muscles, vascular endothelium, and smooth muscle

OTHER HIGH YIELD POINTS

- Mostly a disease of childhood due to **nucleotide 3243 mutation**



High-power image depicting necrosis

- Presents with recurrent stroke-like episodes with relatively normal intervals in between episodes
- In addition to hemiplegia and hemianopia, patients can also have seizures
- Lactic acidosis and myopathy are variable in severity

Path Presenter

MYOCLONIC EPILEPSY WITH RAGGED RED FIBERS (MERRF)

MORPHOLOGY

- Gross: In many cases, the brain appears macroscopically unremarkable
    - ➢ Discoloration of dentate and inferior olivary nuclei may be seen
- Microscopy:
    - ➢ Neuronal dropout and gliosis in dentate nucleus, olives, red nuclei, basal ganglia, locus ceruleus, substantia nigra, and tegmentum of pons
    - ➢ Skeletal muscle shows myopathic changes with aggregates of abnormal mitochondria

OTHER HIGH YIELD POINTS

- Maternal inheritance with a point mutation in mt-tRNA

Manifests in young adults or children with myoclonic epilepsy, mental retardation, myopathy with ragged red fibers, and in some cases sensorineural hearing loss

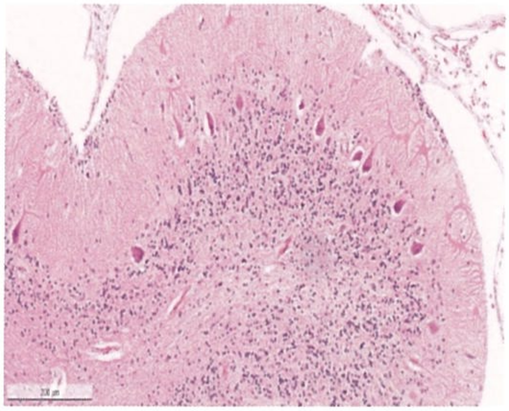
KEARNS-SAYRE SYNDROME (KSS) AND CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (CPEO)

MORPHOLOGY

- Gross: Slight discoloration of involved white matter
- Microscopy:
    - ➢ White matter in the brainstem and cerebellum shows spongy degeneration and vacuolation
    - ➢ Oligodendrocyte degeneration can be seen in severe cases
    - ➢ Thickening and mineralization of blood vessels in basal ganglia, midbrain, thalamus, and dentate nucleus is present in some cases
    - ➢ Skeletal muscles show a ragged red appearance with abnormal mitochondrial accumulation
        - ▪ Abnormal mitochondrial accumulations can be seen in histochemical and electron microscopic examinations
        - ▪ Cytochrome oxidase is negative in many muscle fibers

OTHER HIGH YIELD POINTS

- KSS is progressive retinopathy and pigmentary retinopathy with onset before 20 years
- Other features like conductive block cardiomyopathy, deafness, and short stature could be present
- CPEO presents with ptosis and ophthalmoplegia
    - ➢ Essentially a component of KSS but lacks other features of that syndrome
- Most commonly sporadic and results from heteroplasmic mtDNA deletion
    - ➢ Some patients with KSS have tandem duplications in mtDNA as well
    - ➢ Patients with CPEO will not have tandem duplications



Purkinje neurons with torpedo-like dendritic swellings

MENKES DISEASE

MORPHOLOGY

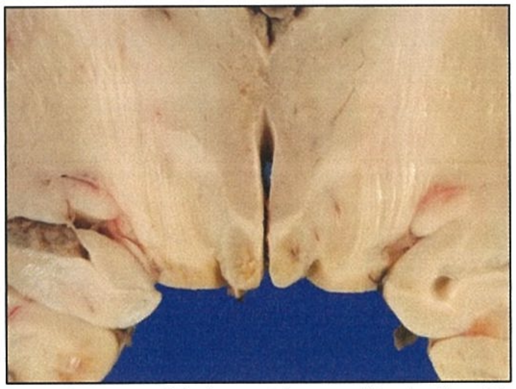
- Gross: Microcephaly and cerebellar atrophy can be seen
- Microscopy:
    - ➢ Lesions in cerebellar cortex with **depletion of granular layer** neurons
    - ➢ **Abnormalities in Purkinje neurons** are seen, which show **bizarre dendritic swellings resembling "torpedoes"**
- Thickened and split elastic layers are seen in the blood vessels

OTHER HIGH YIELD POINTS

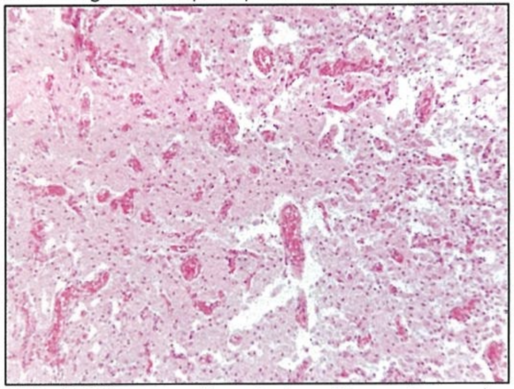
- **X-linked** disease with **abnormalities in copper metabolism** with resultant low levels of copper and ceruloplasmin in the blood
- Also called **steel/ kinky hair disease**
- Manifests as neuropsychiatric symptoms and abnormal hair morphology

Path Presenter

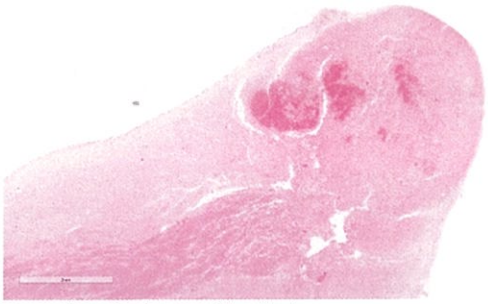
VITAMIN DEFICIENCIES



Coronal section of the brain with mammillary bodies with a discrete erythematous appearance, as well as hemorrhage of the septum pellucidum



H&E (100X), mammillary body with great vascular proliferation with disintegration and edema of the neuropil. Picture courtesy: Dr. Erick Gomez Apo, MD

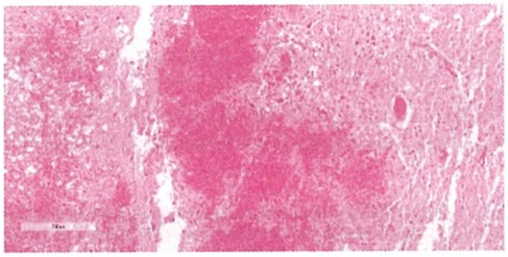


Hemorrhage in the mamillary body

THIAMINE (VITAMIN B1) DEFICIENCY

MORPHOLOGY

- Grossly, mammillary bodies are most frequently affected (shrunken, discolored, and hemorrhagic)
- Other regions of the brain including the medial thalamus, periaqueductal gray matter, inferior olives, floor of the 3rd ventricle, etc. can also be involved
- Microscopy:
  - Acute lesions show edema, hemorrhage, and necrosis of surrounding tissue with sparing of neurons
  - Vascular hyperplasia can be seen with perivascular hemosiderin deposition
  - Chronic lesions show gliosis, demyelination, hemosiderin deposition, and mild neuronal dropout



Higher power showing hemorrhagic necrosis and hemosiderin deposition in mammillary body

OTHER HIGH YIELD POINTS

- Can be due to decreased intake, alcoholism, chronic diarrhea, prolonged parenteral nutrition, or rarely genetic defects in absorption
- Ataxia or gaze palsies can be the presenting symptoms
- Wernicke encephalopathy: Confusion, apathy, and delirium
  - Reversible, but if left untreated can progress to psychosis
- Wernicke-Korsakoff syndrome: Retrograde and anterograde amnesia which leads to confabulation; is irreversible
- "Beriberi" is the term used for the severe chronic form of peripheral neuropathy

Path Presenter

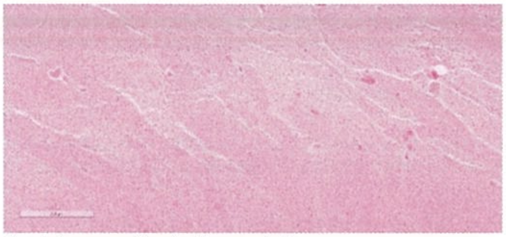
COBALAMIN (VITAMIN B12) DEFICIENCY

MORPHOLOGY

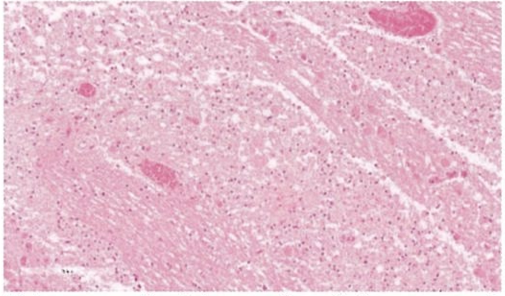
- Gross: Spinal cord posterior and lateral columns show discoloration and possible shrinkage
- Microscopy:
  - Demyelination and vacuolation of white matter are seen in posterior and lateral spinal columns
  - Tract degeneration, pigment-laden macrophages, and gliosis are seen with disease progression
  - Pathology can extend to other white matter areas in the spinal cord with increasing severity of the disease, as well as the optic nerve and cerebral white matter

OTHER HIGH YIELD POINTS

- Usually due to reduced dietary intake of B12 or absent/defective intrinsic factor
- Rarely secondary to *Diphyllobothrium latum* infestation or intestinal bacterial overgrowth
- Syndrome of nervous system involvement is called "subacute combined degeneration"



Tract degeneration in the medulla



Higher power of tract degeneration with the presence of spheroids

VITAMIN E DEFICIENCY

MORPHOLOGY

- Gross: Mostly no gross abnormalities
- Microscopy: Axonal swelling and degeneration in ends of long axons along with neuronal dropout and lipofuscinosis in the remaining neurons
  - ➢ Seen in peripheral nerves, corticospinal tracts, dorsal root ganglia, and brainstem nuclei

OTHER HIGH YIELD POINTS

- Most common cause of deficiency is GI or pancreaticobiliary dysfunction
  - ➢ Patients with cystic fibrosis, celiac disease, etc. are prone
- Neurologic manifestations include peripheral neuropathy, spinocerebellar ataxia, nystagmus, and decreased position and vibration sense
- Hematologic manifestations include hemolytic anemia and acanthocytosis

Path Presenter

TOXICITIES

CARBON MONOXIDE TOXICITY

MORPHOLOGY

- Gross:
  - ➢ In cases of death within a few hours of intoxication, diffuse swelling with cherry red congestion and petechial hemorrhages
  - ➢ When there is a week or more between exposure and death, bilateral globus pallidus necrosis is seen
- Microscopy:
  - ➢ Ischemic or hemorrhagic necrosis of bilateral globus pallidus
  - ➢ Neuron loss is seen in cerebral and cerebellar cortices and the hippocampus
  - ➢ Demyelination with necrosis and axonal sparing is seen in white matter
  - ➢ Chronic lesions show gliosis and cavitations

OTHER HIGH YIELD POINTS

- CO toxicity occurs by inhaling products of incomplete combustion of carbon-containing substances
- Can be suicidal, accidental, or homicidal
- Symptoms arise from decreased oxygen-carrying capacity of blood and interaction of CO with iron/heme-containing proteins like hemoglobin, myoglobin, cytochromes, etc.
- Vulnerability of pallidal neurons and the relatively high iron content of this area make globus pallidus a highly affected area
- Symptoms depend on the duration and concentration of CO exposure and include headache, cough, visual problems, psychotic disturbances, seizures, coma, and death

ETHANOL TOXICITY

MORPHOLOGY

- Gross:
  - ➢ In acute intoxication, petechiae, congestion, and edema are usually the only grossly visible pathology
  - ➢ Cerebral and cerebellar atrophy are seen in cases of chronic ethanol use
  - ➢ Cerebellar atrophy is more pronounced in the superior cerebellar vermis
- Microscopy:
  - ➢ Atrophy with sulcal widening can be seen in both cerebral and cerebellar hemispheres
  - ➢ Neuronal loss and gliosis involving inferior olivary nuclei
  - ➢ Deep cerebellar nuclei can also show degenerative changes
  - ➢ Certain cases show central pontine myelinolysis

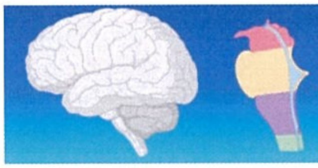
OTHER HIGH YIELD POINTS

- Acute intoxication occurs when large amounts of ethanol are consumed
- More than 450-500 mg/dL is considered lethal and results in death from cardiorespiratory paralysis
- Chronic ethanol consumption results in direct toxicities like Marchiafava-Bignami disease, central pontine myelinolysis, etc., as well as indirect adverse effects secondary to associated nutritional deficiencies like Wernicke encephalopathy, Wernicke-Korsakoff syndrome, pellagra, etc.

METHANOL TOXICITY

MORPHOLOGY

- Gross: Edema of the optic disc along with edema and necrosis of the optic nerve are characteristic findings
- Microscopy:
  - ➢ Generalized hypoxic/ischemic changes in the cerebral cortex with white matter necrosis are seen
  - ➢ Varying degrees of hemorrhagic necrosis of putamen with cavitation, histiocytic inflammation, and gliosis
  - ➢ Edema and necrosis of optic disc and optic nerve



OTHER HIGH YIELD POINTS

- Most common poisoning scenario is drinking as a substitute for ethanol
- Methanol is neurotoxic, as are its metabolic byproducts formaldehyde and formic acid
- Clinical manifestations include metabolic acidosis, nausea, vomiting, abdominal pain, and loss of vision
- Severe poisoning can result in delirium, coma, and sudden death

HEPATIC ENCEPHALOPATHY

MORPHOLOGY

- Gross: Yellowish-green discoloration of the dura, choroid plexus, and brain in the setting of jaundice
- Microscopy:
  - In acute cases, Alzheimer type II astrocytes are the only microscopic finding
    - Large vesicular nuclei and scant cytoplasm
    - Seen in the cortex, basal ganglia, brainstem, deep gray nuclei, and dentate nucleus
  - Chronic cases show microcavitation and necrosis in the gray-white junction
  - Corticospinal tract degeneration, neuronal dropout, and gliosis are seen
  - Opalski cells, astrocytes with granular eosinophilic cytoplasm and small central nuclei, are seen in Wilson disease-associated hepatic encephalopathy
  - Occasionally seen in other causes of hepatic encephalopathy

OTHER HIGH YIELD POINTS

- Secondary to liver failure or portocaval shunting resulting in hyperammonemia
- Symptoms include asterixis, bad breath (fetor hepaticus), drowsiness, memory problems, gait disturbances, and spasticity (hepatic myelopathy)
- Severity can range from chronic hepatic encephalopathy with neurologic disturbances, ataxia, and choreoathetosis to a rapidly progressive fatal form

HEAVY METAL TOXICITIES

ALUMINUM

MORPHOLOGY

- Gross: Macroscopically unremarkable
- Microscopy:
  - Mild gliosis with microglial activation
  - Neuritic and synaptic damage to pyramidal neurons in the hippocampus; neurofibrillary tangles are not seen
  - Special stains can demonstrate aluminum-containing depositions in choroid epithelium and brainstem neurons

OTHER HIGH YIELD POINTS

- Mostly related to chronic dialysis
- Presents as speech and gait disturbance, focal seizures, and in some cases dementia
- Aluminum accumulates in the cortex from prolonged, high-level exposure

ARSENIC

MORPHOLOGY

- Gross: Edematous brain with scattered petechial hemorrhages
- Microscopy: Fibrinoid necrosis of blood vessels, often with surrounding mixed inflammation and hemorrhage

OTHER HIGH YIELD POINTS

- Accidental ingestion of insecticides/weed killers containing arsenicals or organic pentavalent arsenicals in some anti-trypanosomal medications are usual exposure routes
- Historic examples of deliberate poisoning
- Acute hemorrhagic leukoencephalopathy seen in ~5% of patients treated with melarsoprol (trypanosomiasis medication) as a hypersensitivity reaction rather than direct toxicity
- Other symptoms include diarrhea, nausea, vomiting, and in extreme cases renal failure and death
- Distal peripheral neuropathy is seen in chronic exposure secondary to vascular pathology in dorsal root ganglia

LEAD

MORPHOLOGY

- Gross: In acute encephalopathy, brain edema, congestion, and hydrocephalus can be seen
- Microscopy:
  - Spongiosis, necrosis, and gliosis are reported in lead toxicity
  - Blood vessels can have thrombosis, necrosis, and endothelial damage
  - Basophilic stippling of RBCs is seen on peripheral smear

OTHER HIGH YIELD POINTS

- Occupational, deliberate, or accidental exposure from lead-containing paints, pipelines, traditional medicines, cosmetics, or gasoline
- It is a potent neurotoxin and chronic exposure to even low levels can result in toxicity
- Acute encephalopathy is the most common manifestation in children
- Insidious onset of lethargy, abdominal cramps, psychiatric symptoms, and seizures can be seen in chronic intoxication, mainly in adults
- Peripheral neuropathy as well as adverse cognitive and motor skills are also noted

- Acute intoxication symptoms usually respond to the removal of the source of exposure and chelation therapy, but residual permanent damage may persist

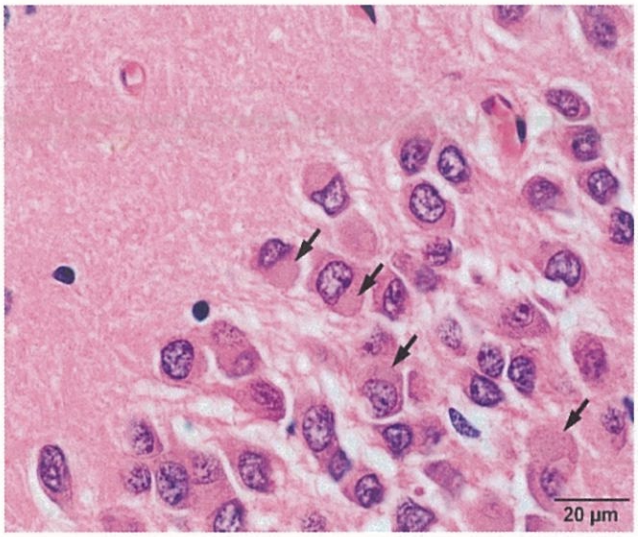
MERCURY

MORPHOLOGY

- Gross:
  - Atrophy of the brain, predominantly the cerebellum and visual cortex, is seen in methylmercury toxicity
  - Usually the brain is grossly unremarkable in inorganic mercury exposures
- Microscopy:
  - Neurons are most affected, with dropout predominantly among small neurons including the granular cell neurons of the cerebellum and neurons in visual and somatosensory layers
  - Granular intralysosomal deposits of mercury can be seen in neurons and glia in long-term patients
  - Associated gliosis and macrophages can be seen
- Fetal brains with exposure can show cortical dysplasia and neuronal heterotopia

OTHER HIGH YIELD POINTS

- Poisoning can be by the organic or inorganic form of mercury
- Neurotoxicity can develop from inhalation of inorganic mercury vapors
- Ingestion of contaminated seafood (Minamata disaster) or food made from grains contaminated with mercury fungicide results in organic mercury intoxication
- Methylmercury is neurotoxic and also results in dysembryogenesis and psychomotor retardation in infants
- Acute toxicity manifests as metallic halitosis, increased saliva, diarrhea, visual and psychotic disturbances, ataxia, and sensory neuropathy
- Chronic toxicity can result in blindness, paralysis, and mental retardation



NEURODEGENERATIVE DISEASES

KATHERINE E. SCHWETYE, MD, PHD
ROGER ALAN FECHER, MD

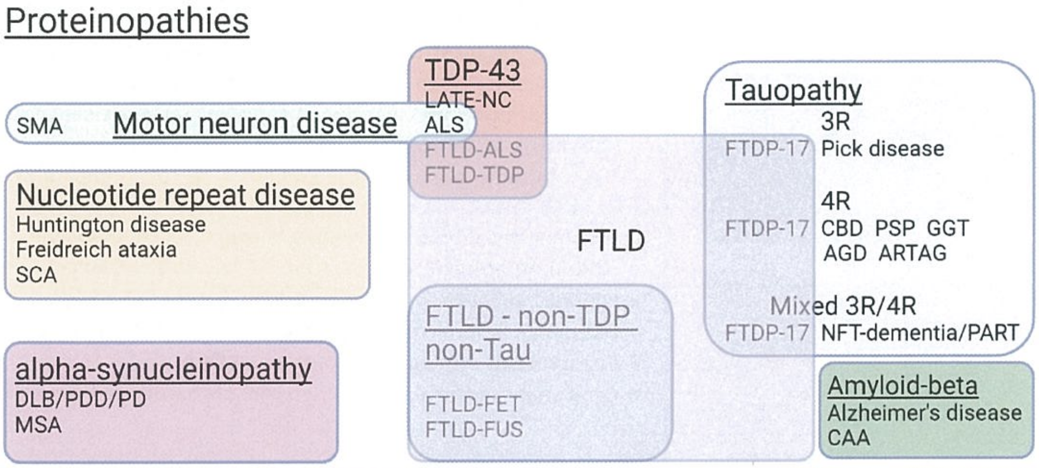
8. NEURODEGENERATIVE DISEASES

NORMAL AGING

- In groups of healthy elderly persons at very low risk of Alzheimer disease (AD), volumetric reductions and ventricular expansion are detectable
- Although most of the brain shows significant volume reductions, areas of greatest change aligned well with the default mode network
- Not all brain changes in aging reflect incipient AD, but rather, volume reductions are a general feature of normal aging
- Maintenance of superior cognitive performance in an oldest-old cohort (The 90+ study) was associated with lower levels/absence of comorbid neuropathologic features in the brain (amyloid plaques, tau, α-synuclein, TDP-43 or vasculopathy)

NEURODEGENERATIVE DISEASE CLASSIFICATION

Historically, neurodegenerative diseases were classified based on clinical presentation and/or anatomical distribution of pathology. Modern approaches more frequently classify neurodegenerative diseases by protein aggregates and/or underlying molecular changes. The graphic below utilizes this modern framework – and illustrates overlap in some categorizations, most notably the frontal temporal lobar degenerations (FTLD). Abbreviations are defined in the chapter.



Proteinopathies

TDP-43
LATE-NC
ALS
FTLD-ALS
FTLD-TDP

SMA Motor neuron disease ALS

Nucleotide repeat disease
Huntington disease
Freidreich ataxia
SCA

FTLD

Tauopathy
3R
FTDP-17 Pick disease
4R
FTDP-17 CBD PSP GGT
AGD ARTAG
Mixed 3R/4R
FTDP-17 NFT-dementia/PART

alpha-synucleinopathy
DLB/PDD/PD
MSA

FTLD - non-TDP
non-Tau
FTLD-FET
FTLD-FUS

Amyloid-beta
Alzheimer's disease
CAA

α -SYNUCLEINOPATHIES

α-synuclein

- Encoded by *SNCA* on chromosome 4
- Protein exists in various conformations in dynamic equilibrium
- Presynaptic protein exists in membrane-bound and free cytoplasmic forms

MORPHOLOGY

- Neuronal inclusions: α-synuclein was discovered to be the primary protein component of Lewy bodies (LBs) and Lewy neurites
  - Brainstem Lewy bodies – round eosinophilic cytoplasmic inclusions with halo (clearly visible on H&E)
  - Cortical Lewy bodies – poorly demarcated, round, amphophilic cytoplasmic inclusions (difficult to visualize on H&E)
  - Pale bodies – faint neuronal cytoplasmic inclusions without a halo; possibly a precursor to a Lewy body
  - Lewy neurites – protein accumulations in axonal processes
- Glial inclusions: α-synuclein is the main component of glial cytoplasmic inclusions (GCIs) of multiple system atrophy (MSA) – primarily seen in oligodendrocytes
- α-synuclein IHC is essential for the identification of Lewy neurites and for the identification of glial

PARKINSON DISEASE (PD), PARKINSON DISEASE DEMENTIA (PDD) AND DEMENTIA WITH LEWY BODIES (DLB)

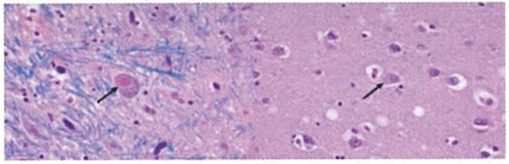
MORPHOLOGY

- Caused by loss of pigmented neurons in the substantia nigra pars compacta (SNpc) and characterized by the presence of inclusions termed Lewy bodies (LBs)
- Grossly, pallor of substantia nigra and locus ceruleus
- Classified by the distribution of Lewy bodies
  - None: No LBs
  - Brainstem-predominant: LBs in the medulla, pons, and/or midbrain
  - Limbic (transition): LBs in cingulate or entorhinal cortex, usually with brainstem involvement
  - Neocortical (diffuse): LBs in frontal, temporal or parietal cortex – usually with involvement of brainstem and limbic sites
  - Amygdala-predominant: LBs in amygdala with no more than a paucity in other areas

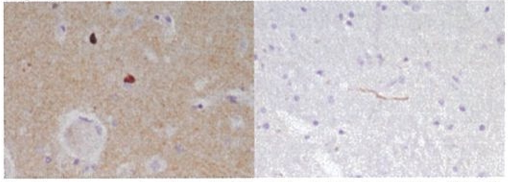
OTHER HIGH YIELD POINTS

- Presentation: slowness of movement, cogwheel rigidity, postural instability and tremors; non-motor symptoms include REM sleep disorder, constipation, and hyposmia, which may precede motor symptoms
- Motor symptoms due mostly to the loss of dopaminergic neurons in the substantia nigra and commensurate dysregulation of basal ganglia activity
- **PDD and DLB** are thought to be two ends on the spectrum of a single disease, which is **distinguished clinically**

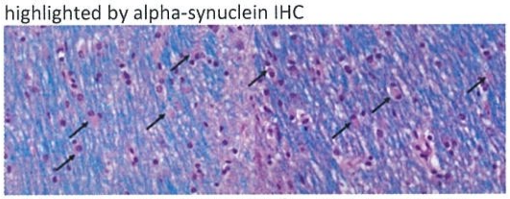
cytoplasmic inclusions, cortical Lewy bodies, pale bodies, and glial and neuronal inclusions in MSA



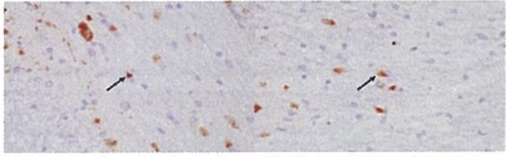
Lewy body in brainstem (left) and cortical Lewy body (right)



Cortical Lewy bodies (left) and Lewy neurites (right) highlighted by alpha-synuclein IHC



Glial cytoplasmic inclusions (GCI) in MSA on LHE stain



Glial cytoplasmic inclusions (GCI) in MSA with alpha-synuclein IHC, arrows highlight classic pointed-hat shaped inclusions

  - ➢ PDD has early Parkinsonism; DLB has none or late onset Parkinsonism
  - ➢ DLB frequently exhibits visual hallucinations

MULTIPLE SYSTEM ATROPHY (MSA)

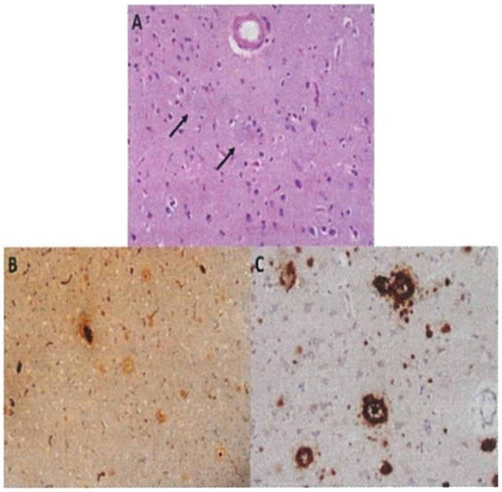
MORPHOLOGY

- Neurodegenerative changes in striatonigral and/or olivopontocerebellar region reflecting clinical disease
- Atrophy and dark discoloration of the putamen, most severe posteriorly
- Pallor of substantia nigra
- Cerebellar atrophy
- Indistinct inferior olivary nucleus (ION)
- **Oligodendroglial inclusions**: widespread and abundant accumulations of α-synuclein form glial cytoplasmic inclusions (GCIs) and glial nuclear inclusions (GNIs)
- **GCIs are the most common** and readily identified inclusions – they are perinuclear inclusions with a cone-like or "pointed-hat" shape
- Neuronal inclusions: neuronal cytoplasmic and nuclear inclusions (NCIs and NNIs) and threads
  - ➢ NCIs are most readily identified in the pons and putamen

OTHER HIGH YIELD POINTS

- Encompasses diseases previously known as olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SDN), and Shy-Drager syndrome (SDS)
- Sporadic, progressive disease in adults (onset after 30 years old)
- Autonomic failure with **orthostasis**
- Parkinsonism with **poor response to L-DOPA**
- Cerebellar syndrome (wide-based gait, uncoordinated movements)

AMYLOID-BETA



Amyloid-β plaques on hematoxylin and eosin (A), Bielschowsky (B), and beta-amyloid IHC (C)

AMYLOID-β

- Aβ is cleaved from amyloid precursor protein (APP) by β-secretase into C99, which is then cleaved by γ-secretase complex (includes presenilin) into Aβ (two forms Aβ40 and Aβ42)

MORPHOLOGY

- Upon aggregation, Aβ may form "amyloid" – a generic term used in pathology to denote proteinaceous tissue deposits with a high content of β-pleated sheet structure
  - ➢ Highlighted by Congo red or thioflavin S
- Parenchymal deposits, or "plaques"
  - ➢ Diffuse deposits – wispy, larger, and less dense than plaques; highlighted by silver stains and Aβ IHC, not visible on H&E
  - ➢ Dense core plaques – consist of a core with a pale ring and an outer diffuse rim of amyloid; visible on H&E and highlighted by silver stains and Aβ IHC
  - ➢ Neuritic plaques – consist of a dense core with a pale ring, diffuse rim of amyloid and peripheral dystrophic neurites - visible on H&E and highlighted by silver stains and Aβ IHC; neurites highlighted by tau IHC

ALZHEIMER'S DISEASE

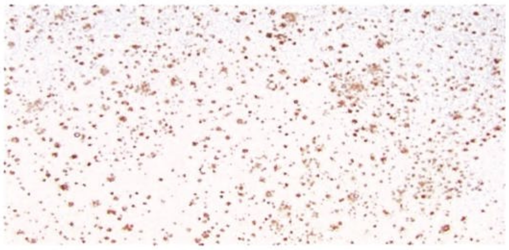
MORPHOLOGY

- Diffuse atrophy – with marked reduction in the medial temporal lobe (temporal pole, amygdala, hippocampus, and fusiform gyrus) and relative sparing of inferior frontal gyri, orbitofrontal gyri, and occipital lobe

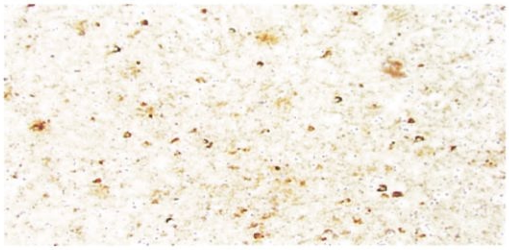
8. NEURODEGENERATIVE DISEASES

- Loss of neurons and synapses in cerebral cortex and subcortical regions
- Alzheimer's pathology is typically a combination of:
    - Diffuse and cored amyloid plaques (use anti-amyloid-β IHC)
    - Neuritic plaques (distinct from amyloid plaques; quantified with silver or tau IHC)
    - Neurofibrillary tangles, including pre- and ghost tangles (visualized with silver or tau IHC) – discussed in more detail in tauopathies (below)
- Other AD-associated findings
    - Granulovacuolar degeneration – accumulation of small, clear vacuoles containing argyrophilic granule; seen in AD as well as Pick disease
    - Hirano bodies – eosinophilic rod-shaped inclusions, composed of actin and actin-binding proteins in dendrites; seen in AD as well as Pick disease
- Alzheimer pathology scored according to the ABC score:
    - Amyloid plaques: use the Thal phase to derive "A" score
    - Neurofibrillary tangles: use the Braak stage to derive "B" score
    - Neuritic plaques: use CERAD methodology to derive "C" score.

NOTE: **Must use Bielschowsky or tau stain, NOT Amyloid-β IHC**



Aβ IHC highlights numerous diffuse deposits and amyloid plaques in the neocortex



Tau immunostain highlights neuritic plaques and neurofibrillary tangles (NFTs)

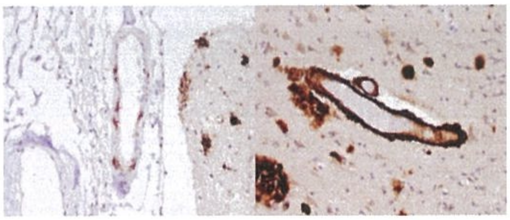
OTHER HIGH YIELD POINTS

- Most common cause of dementia
- Dementia – decline in daily functioning due to cognitive impairment (contrast with mild cognitive impairment, which doesn't impair daily function)
- Dementia may be presenile or senile
    - Early onset AD (EOAD) is more often familial
    - ABC score is then used to determine the level of neuropathologic change (not, low, intermediate, high), using the following table:

ABC score			
A score (amyloid)	Thal Phase	B score	Braak NFT stage
0	0	0	None
1	1 or 2	1	I or II
2	3	2	III or IV
3	4 or 5	3	V or VI
C score		CERAD score neuritic plaques	
0		None	
1		Sparse (1-5 neuritic plaques/1mm^2)	
2		Moderate (>/ 6 and <20 neuritic plaques/1mm^2)	
3		Frequent (>/ 20 neuritic plaques/1mm^2)	

AD neuropathologic change		B score (Braak stage)		
A score (amyloid)	C score (CERAD)	0 or 1	2	3
0	0	Not	Not	Not
1	0 or 1	Low	Low	Low
	2 or 3	Low	Intermediate	Intermediate
2	Any C	Low	Intermediate	Intermediate
3	0 or 1	Low	Intermediate	Intermediate
	2 or 3	Low	Intermediate	High

- For individuals without cognitive impairment, it should be noted that neuropathologic changes can predate the onset of symptoms by years
- For individuals with cognitive impairment, "Intermediate" or "High" disease should be considered adequate to explain cognitive impairment
- Standardized work-up of all cases should include assessment of cerebral amyloid angiopathy
- Co-morbid pathologies (α-synuclein, TDP-43, vasculopathy) are the rule rather than the exception



Cerebral amyloid angiopathy, mild (left) and moderate (right) with Aβ IHC

AMYLOID ANGIOPATHY

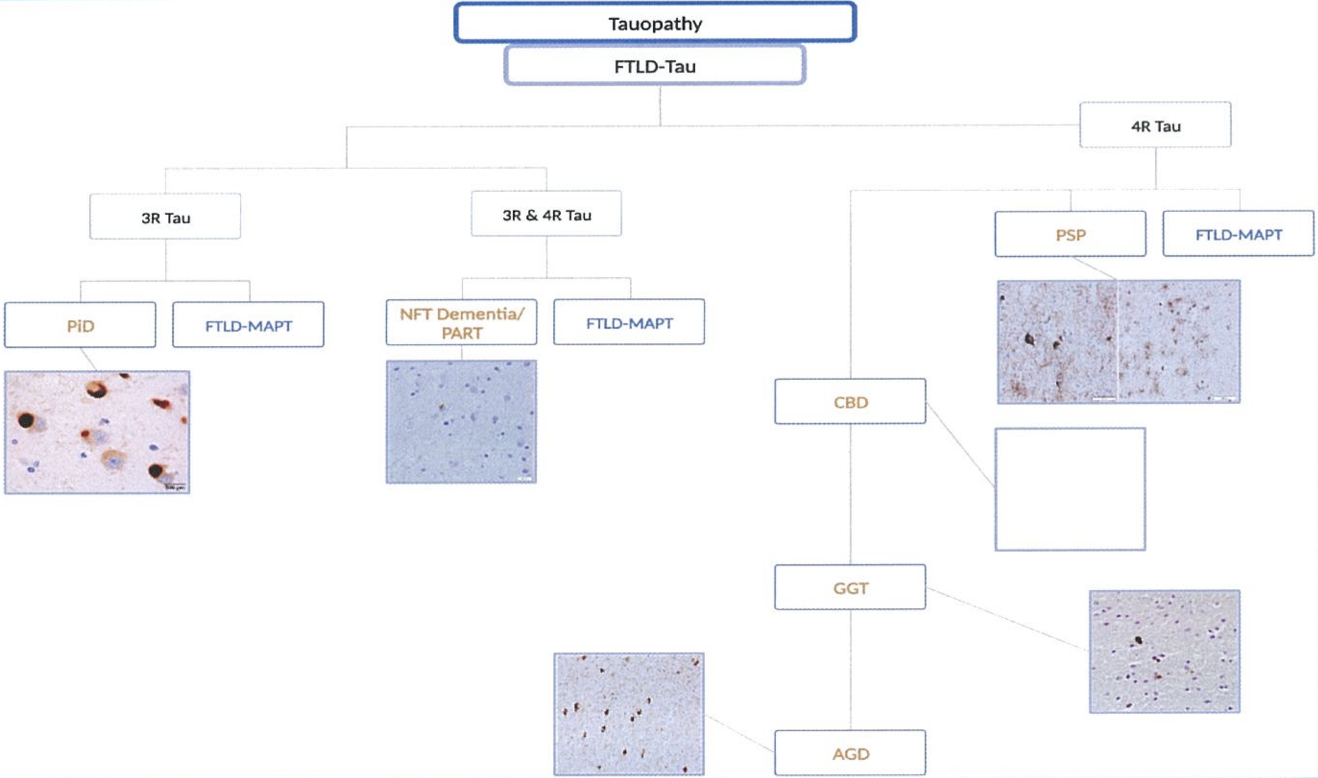
MORPHOLOGY

- Accumulation of Aβ in the vessel walls
- Primarily seen in the neocortex – and later in Ammon's horn and cerebellum
- May occur in the absence or presence of Alzheimer's disease

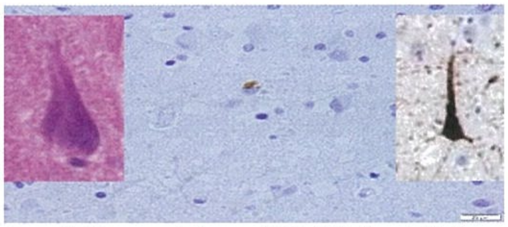
OTHER HIGH YIELD POINTS

- Vonsattel criteria for cerebral amyloid angiopathy (CAA) grading:
  - No CAA = No staining
  - Mild CAA = Patchy amyloid deposition
  - Moderate CAA = circumferential amyloid deposition
  - Severe CAA = fibrinoid necrosis leads to vessel-within-vessel amyloid staining pattern, so-called "double barrel" or "stovepipe" pattern

TAUOPATHIES



TAUOPATHIES – PATHOLOGY



Neurofibrillary tangle; insets: H&E of NFT (top left), Tau-stained NFT (top right)

TAU

- Tau protein is the most abundant neuronal microtubule-associated protein
- Encoded by the ***MAPT* gene** on chromosome 17
- There are six isoforms formed by alternative splicing of mRNA
- Exon 10 encodes a repeat-containing sequence of the microtubule-binding domain, which gives rise to either 3- or 4-repeat tau (3R and 4R tau)

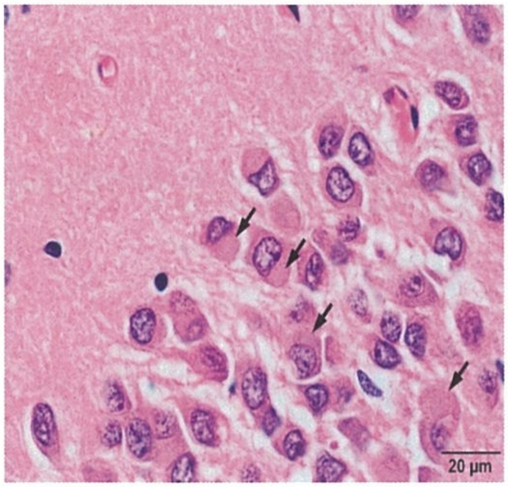
MORPHOLOGY

- Intracellular **accumulations within neurons and glia**
- Neurons – contain neurofibrillary tangles, threads, and argyrophilic grains
  - Pretangle – diffuse or granular, cytoplasmic, non-fibrillar tau
  - Neurofibrillary tangles – intracellular accumulation of fibrillar hyperphosphorylated tau within the cell body
  - Threads – short, tortuous tau accumulation in cell processes
  - Argyrophilic grains – spindle-shaped inclusions in neuronal processes found in cortical and subcortical areas

- Astrocytes - there are a wide variety of astrocytic lesions, many considered specific for certain disease entities (see diseases below for additional information). Astrocytic inclusions include (but are not limited to): ramified astrocytes, astrocytic plaques, tufted astrocytes, protoplasmic astrocytes, globular astroglial inclusions, "bush-like" astrocytes, coiled bodies

OTHER HIGH YIELD POINTS

- Clinically, morphologically, biochemically heterogeneous neurodegenerative diseases



Pick's disease - Ballooned neurons (hippocampus)

3R TAUOPATHY - PICK'S DISEASE

MORPHOLOGY

- Previously used to refer to the clinical diagnosis of frontotemporal dementia (FTD), currently reserved for specific pathologic findings of neuronal intracellular hyperphosphorylated 3R tau "Pick bodies"
- Pick cells (ballooned or swollen cells) and Pick bodies (intracellular inclusions, randomly arranged 3R tau filaments) – detected particularly in the granule cells of the dentate gyrus
- Severe loss of pyramidal neurons in cortical layers II, III, and IV also seen; synaptic density loss in superficial frontal layers
- Severe cortical **"knife-edge" atrophy** – characteristically in the frontal and temporal lobes
- Bilateral atrophy but **frequently asymmetrical**

HIGH YIELD POINTS

- Majority present with behavioral variant frontotemporal dementia
- Others present with progressive non-fluent aphasia or semantic dementia
- FTDP-17 – can be 3R, 4R, or mixed

MIXED 3R + 4R TAUOPATHY

PRIMARY AGE RELATED TAUOPATHY (PART)

MORPHOLOGY

- **"Tangle only" dementia**: NFTs found in the absence of neuritic plaques
- Describes pathologic continuum from focal (medial temporal) NFTs in cognitively normal to widespread cortical NFTs (in the absence of neuritic plaques)
- Graded using Braak stages, but rarely progresses to Braak V or VI (since cortex is rarely involved)

OTHER HIGH YIELD POINTS

- The relationship between AD and PART is unclear
- A correlation been severe PART and memory loss has been noted, but the high prevalence of comorbid brain diseases in the elderly population makes clinicopathological correlation challenging

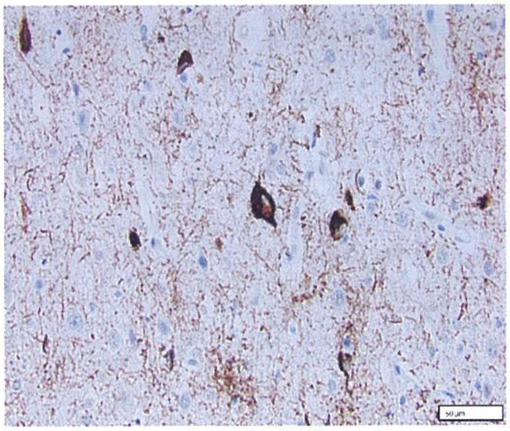
4R TAUOPATHY- CORTICOBASAL DEGENERATION (CBD)

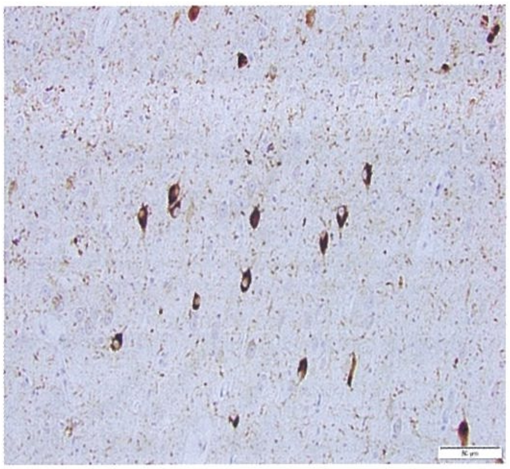
MORPHOLOGY

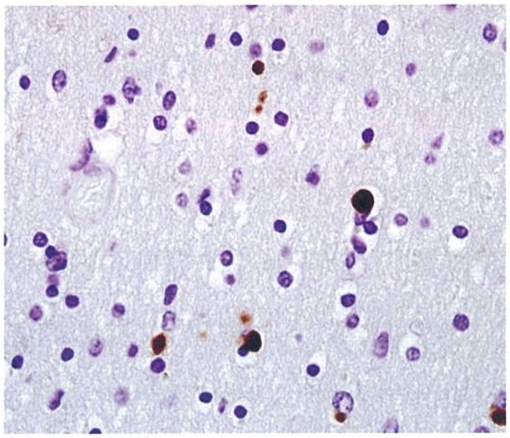
- Focal and asymmetric cortical atrophy mostly in superior frontal or parietal parasagittal, pre- and postcentral regions
- Atrophy in superior frontal and parietal parasagittal regions
- Red-brown discoloration of the globus pallidus
- Pallor of substantia nigra
- Atrophy and flattening of the caudate nucleus
- Subthalamic nucleus preserved; brainstem not atrophic
- Substantia nigra shows depigmentation, neuronal loss, and gliosis in cases with motor symptoms
- Neuronal loss and gliosis in cortical and subcortical areas
- Cortex: ballooned, achromatic neurons
- Most specific: the astrocytic plaque (gray matter), an annular cluster of short stubby processes representing the distal segment of astrocytic processes
- Diffuse granular cytoplasmic tau immunoreactivity of neurons, threads, and small spherical cytoplasmic bodies (corticobasal bodies), particularly in the substantia nigra
- Oligodendroglial coiled bodies

OTHER HIGH YIELD POINTS

- Driven by the distribution of pathology
  - ➢ Cortical pathology causes frontal lobe dementia, progressive rigidity and apraxia, non-fluent aphasia and apraxia of speech
  - ➢ Subcortical pathology causes atypical parkinsonism and progressive cerebellar ataxia


Progressive supranuclear palsy (PSP)


Argyrophilic grain disease (AGD)


Globular glial tauopathy (GGT)

4R TAUOPATHY - PROGRESSIVE SUPRANUCLEAR PALSY (PSP)

MORPHOLOGY

- Most characteristic: **globose neurofibrillary tangle** in brainstem nuclei and nucleus basalis of Meynert
- Neuropil threads, predominantly in subcortical regions; most numerous in pencil fibers of the striatum and the white matter tracts in and around the subthalamic nucleus
- **Tufted astrocytes** – intracytoplasmic tau aggregates, most prominent glia in the striatum and precentral gyrus
- Less specific pathological findings include:
    - ➢ Coiled bodies in oligodendrocytes (coil or comma-like inclusions)
    - ➢ Balloon neurons (aka Pick cells) – swollen cortical neurons which are often seen in lower cortical layers and most common in limbic and paralimbic systems
- Cortical and white matter involvement is relatively mild
- Pallor of substantia nigra

OTHER HIGH YIELD POINTS

- Driven by distribution of pathology
    - ➢ Cortical pathology causes frontal lobe dementia, progressive rigidity and apraxia, non-fluent aphasia, and apraxia of speech
    - ➢ Subcortical pathology causes atypical parkinsonism and progressive cerebellar ataxia
- Cognitive symptoms correlate with cortical involvement
- Clinically indistinguishable from CBD

4R TAUOPATHY - ARGYROPHILIC GRAIN DISEASE (AGD)

MORPHOLOGY

- **Essential for diagnosis: Argyrophilic grains** are spindle or comma-shaped inclusions within neuronal processes, distributed throughout the neuropil; most abundant in the limbic system
- May be seen: Coiled bodies – perinuclear oligodendroglial inclusions, pre tangles
- No changes in early disease; **selective severe atrophy of the ambient gyrus** may be seen in late-stage disease with relative sparing of the temporal cortex and hippocampus

OTHER HIGH YIELD POINTS

- Most commonly presents with a slowly progressive amnestic syndrome

4R TAUOPATHY - GLOBULAR GLIAL TAUOPATHY (GGT)

MORPHOLOGY

- Widespread **globular glial inclusions (GCIs)** in both oligodendrocytes and astrocytes – form globular, cord-like, or horseshoe-shaped inclusions

OTHER HIGH YIELD POINTS

- Variable clinical presentation
- There are three subtypes (white-matter involvement is a prominent feature in all types)
    - ➢ FTD type: associated with frontotemporal distribution of GCIs
    - ➢ Motor type: associated with pyramidal tract distribution of GCIs
    - ➢ Combination of frontotemporal and motor involvement

FRONTOTEMPORAL LOBAR DEGENERATION (FTLD)

MORPHOLOGY

- Some are tauopathies; others show TDP-43, FUS, and others

OTHER HIGH YIELD POINTS

AGE-RELATED TAU ASTROGLIOPATHY (ARTAG)

MORPHOLOGY

- Characterized by anatomical distribution, location (subpial, subependymal, gray matter, white matter, perivascular), severity, and extent
- Predominantly affects elderly
- Astrocytic tauopathy with distinct morphologies

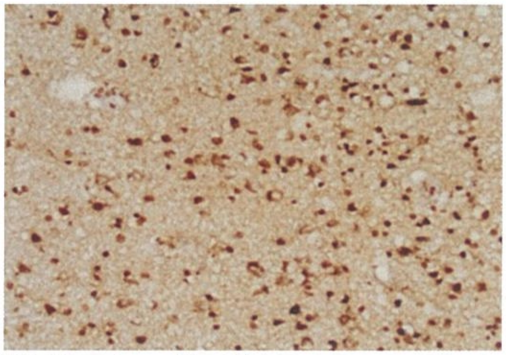
- Neurodegenerative disorder characterized by progressive changes in behavior, personality, and language
- Involves frontal and temporal regions
- ~40% of FTD cases have a positive family history
- ~10% inherited in an autosomal-dominant pattern
- Gene defects present with distinct clinical phenotypes: *MAPT*, *GRN*, *C9orf72*, *VCP*, *CHMP2B*, *TARDBP*, *FUS*, *SQSTM1*, *UBQLN2*, *TBK1*, *TREM2*, and *CHCHD10*
- FTD-ALS is the most heritable clinical syndrome, and svPPA is the least heritable
- **Thorny astrocytes**
  - ➢ Seen especially in subpial and subependymal regions
  - ➢ Exhibit a few short processes and a small eccentric nucleus
  - ➢ Tau-positive by IHC
- **Granular-fuzzy astrocytes**
  - ➢ Frequently in gray matter

OTHER HIGH YIELD POINTS

- Uncertain clinical significance

FTDP-17 – can be 3R, 4R, or mixed

TDP-43


TDP-43 showing positive staining

TDP-43 PROTEINOPATHIES

MORPHOLOGY

- TAR DNA binding protein 43 kDa (TDP-43)
- Highly conserved, ubiquitously expressed nuclear protein; function depends on being shuttled between the nucleus and cytoplasm
- Important for transcriptional repression, RNA splicing, mRNA transport, microRNA maturation, translational regulation, and stress-granule formation
- Hyperphosphorylated and ubiquitinated TDP-43 inclusions represent a major pathological feature of:
  - ➢ Amyotrophic lateral sclerosis (ALS) in >90% of cases, and some forms of frontotemporal lobar degeneration (FTLD)
  - ➢ At least 11 distinct chromosomal loci linked to ALS; mutations in Cu/Zn superoxide dismutase (SOD1), alsin, dynactin, TDP-43, FUS, C9orf72 hexanucleotide repeat expansion
  - ➢ Limbic predominant age-related TDP-43 encephalopathy (LATE) and hippocampal sclerosis

OTHER HIGH YIELD POINTS

TAR DNA binding protein 43 kDa (TDP-43) may be associated with Alzheimer's disease (AD), chronic traumatic encephalopathy (CTE), Lewy body disease (LBD), Huntington's disease, argyrophilic grain disease (AGD)

FRONTOTEMPORAL LOBAR DEGENERATION -TDP

MORPHOLOGY

- Most frequent form of FTLD (50%)
- Majority have concomitant hippocampal sclerosis
- Inclusions mostly in frontotemporal neocortex and dentate granule cells of the hippocampus
- Atrophy in frontal and temporal lobe with sparing of parietal and occipital lobes
- Consists of multiple subtypes with characteristic distribution of cortical and white matter pathology

OTHER HIGH YIELD POINTS

- FTLD presents as one of several syndromes:
  - ➢ Behavioral variant FTD (bvFTD): most frequent phenotype, behavioral-dysexecutive disorder
  - ➢ Distinct language disorders, including primary progressive aphasia (PPA)
  - ➢ Non-fluent/agrammatic variant (naPPA)
  - ➢ Semantic variant (svPPA)
  - ➢ Logopenic variant (lvPPA)
- Distribution of pathology is specific for various subtypes
- Type A – neuronal cytoplasmic inclusions, dystrophic neurites, and occasional neuronal intranuclear inclusions; **genetic association: *GRN***
- Type B – numerous neuronal cytoplasmic inclusions, few dystrophic neurites, and no neuronal intranuclear inclusions; **genetic association: *C9orf72***
- Type C – largely consists of dystrophic neurites
- Type D – numerous neuronal intranuclear inclusions and dystrophic neurites with few neuronal cytoplasmic inclusions; **genetic association: *VC***

HIPPOCAMPAL SCLEROSIS (HS)

- Neuronal loss and gliosis limited to the CA1 sector of the hippocampus without evidence of ischemia or seizures
- TDP-43 containing inclusions are common

8. NEURODEGENERATIVE DISEASES

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

MORPHOLOGY

- Diffuse muscle atrophy
- Spinal cord atrophy, most prominent in cervical and lumbar segments
- Motor neuron loss with cytoplasmic inclusions (TDP-43 is a major protein)
  - ➢ **Inclusions are positive for TDP-43 in >95% of cases**
  - ➢ A minority of cases are negative for TDP-43 and are associated with pathogenic mutations in *SOD1* or *FUS*
- Glial and neuronal inclusions – most characteristic neuronal inclusions described below
  - ➢ **Skein-like inclusions** – intracytoplasmic filamentous inclusions (TDP-43 positive)
  - ➢ **Bunina bodies** – eosinophilic intracytoplasmic inclusions in MNs in familial and sporadic ALS; immunoreactive for cystatin C

OTHER YIELD POINTS

- Loss of upper and lower motor neurons and degeneration of corticobulbar/corticospinal tracts
- Lower motor neuron loss can lead to atrophy, muscle weakness, and fasciculations
- Upper motor neuron loss can lead to hyperreflexia and spasticity
- Leads to death within 3-5 years of symptom onset
- Historically considered a motor neuron disease, but increasingly recognized to be a multisystem disorder with increased vulnerability of motor neurons
- A significant portion will develop frontotemporal syndrome, raising the question if FTLD-TDP and ALS exist on a spectrum

LATE-NC (Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes)

MORPHOLOGY

- Marked neuronal loss and gliosis in the hippocampus with the relatively restricted neuroanatomic distribution of TDP-43
  - ➢ Stage 1: Amygdala only
  - ➢ Stage 2: Amygdala and hippocampus
  - ➢ Stage 3: Amygdala, hippocampus, and middle frontal gyrus

OTHER HIGH YIELD POINTS

- Mimics Alzheimer's disease
- Affects older people (**age > 80 years**)

FRONTOTEMPORAL LOBAR DEGENERATION (FTLD) – non-tau and non-TDP43

FTLD-FET

- 5-10% of FTLD cases

MORPHOLOGY

- Inclusions are negative for tau and TDP-43, but contain the following proteins:
  - ➢ Fused in sarcoma (FUS)
  - ➢ Ewing sarcoma (EWS)
  - ➢ TAT-binding protein-associated factor 15 (TAF15)

- FTLD presents as one of several clinical syndromes – see FTLD-TDP for list of subtypes
- In some cases of FTLD, the inclusions are negative for Tau and TDP43

FTLD-UPS

MORPHOLOGY

- Inclusions are negative for tau, TDP-43, and FUS
- **Mutation in CHMP2B gene**

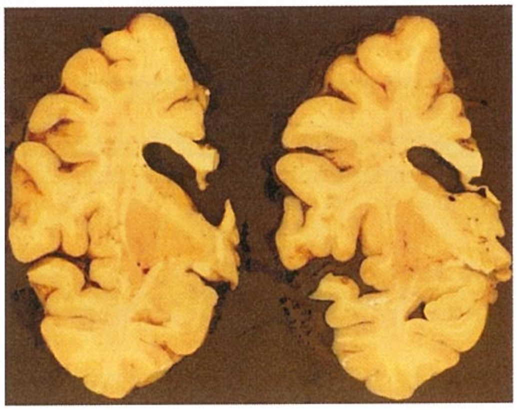
NUCLEOTIDE REPEAT DISORDERS

HUNTINGTON DISEASE

- CAG trinucleotide in the *huntingtin* gene
- Autosomal dominant inheritance

MORPHOLOGY

- Prominent cell loss in the caudate and putamen
- No atrophy in early disease to diffuse atrophy in end-stage disease
- Atrophy in globus pallidus, diencephalon, brainstem, and cerebellum in advanced disease
- Grading system of HD pathology was developed by Vonsattel and comprises 5 severity grades of cellular degeneration:
  - ➢ Grade 0—normal on gross examination, but 30–40% of neurons lost in the head of the caudate nucleus
  - ➢ Grade 1—a 50% neuronal loss in the head of the caudate nucleus, with neuronal loss and astrogliosis evident in the tail +/– body of the caudate nucleus
  - ➢ Grade 2—striatal atrophy, with ventricular profile of the caudate nucleus less convex than normal



Autopsy sections: left hemibrain showing caudate

  - Grade 3—severe striatal atrophy with flat ventricular profile of the caudate nucleus
  - Grade 4—atrophy of the striatum and up to 95% neuronal loss, with a concave ventricular profile of the caudate nucleus

OTHER HIGH YIELD POINTS

- Normal individuals < 36 CAG repeats (~15-25 repeats)
- Chorea – involuntary movements of voluntary muscles
  - Clumsiness in everyday activities, especially walking
- End-stage: akinetic-rigid disorder
- Repeats between 27-35 are unstable during meiosis, which can lead to a new expansion of CAG repeats
- When repeats are present in the pathogenic range, repeat expansion inherited by children leads to "genetic anticipation"
- When >38 repeats, most are predicted to develop HD
- Individuals with <40 repeats may manifest symptoms later
- Number of CAG repeats correlates inversely with the age at symptom onset
- Extremely long CAG repeats (> 60) are highly associated with early onset HD (juvenile HD)

FRIEDREICH ATAXIA

MORPHOLOGY

- Dorsal root ganglia and dorsal horns of the spinal cord, the dentate nuclei of the cerebellum, and the spinocerebellar and corticospinal tracts affected
- Neuropathology of FRDA is thought to result from a combination of abnormal development and progressive degeneration
- Spinal cord thin at all levels, most evident in thoracic segments
- Diminutive dorsal spinal roots

OTHER HIGH YIELD POINTS

- Most common hereditary ataxia
- Progressive dysarthria, dysphagia, and ataxic gait
- **Symptoms typically first manifest around puberty**; onset can occur anytime from infancy through midlife
- Disabling course leading to premature mortality
- Mutation consists of a GAA trinucleotide repeat expansion in the *FXN* gene on 9q21

SPINOCEREBELLAR ATAXIA (SCA)

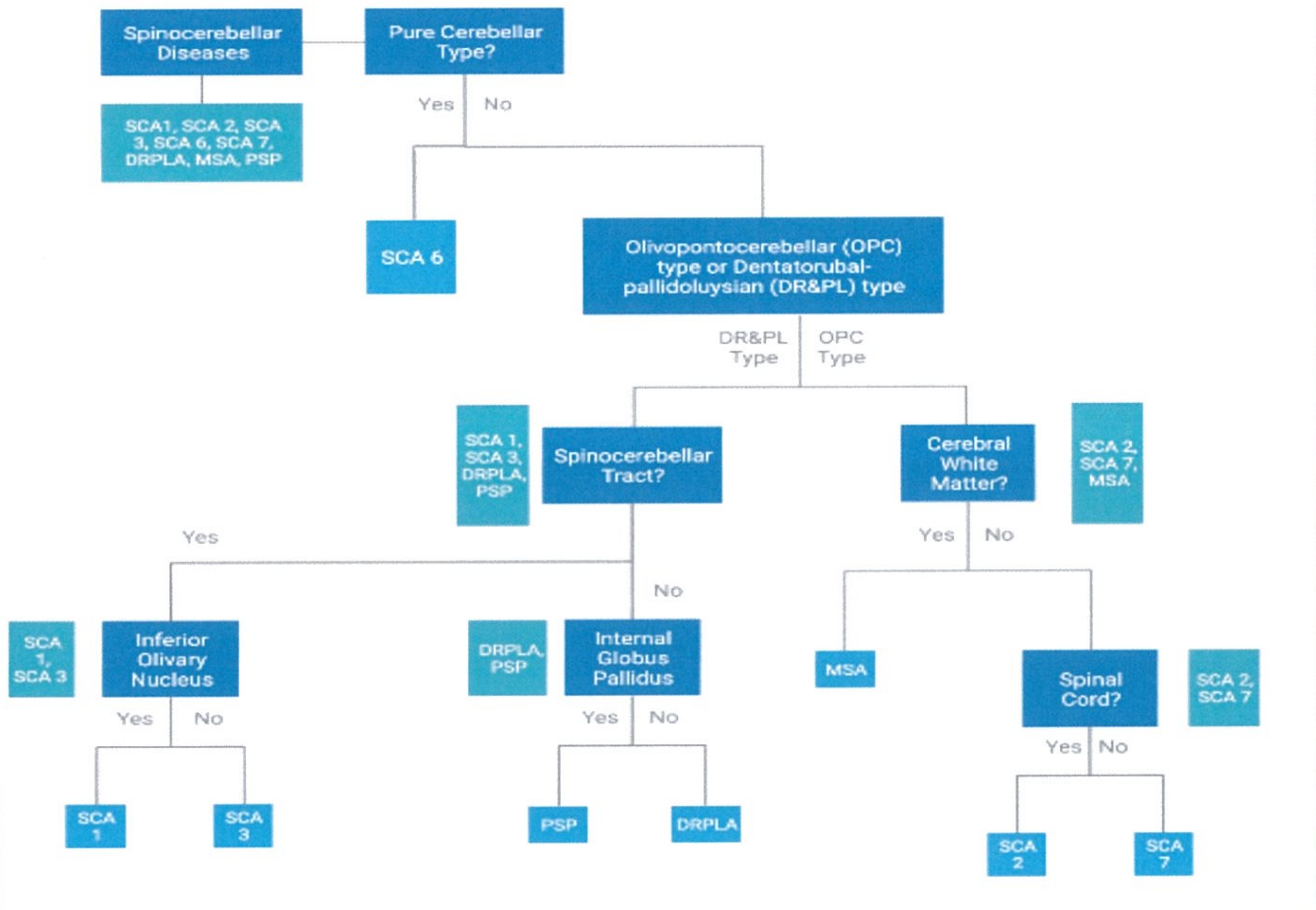
MORPHOLOGY

- Gross findings can classify SCAs (and additional spinocerebellar degeneration disorders) into three major groups:
  - Pure cerebellar type for SCA6 and SCA31
  - Olivopontocerebellar (OPC) type for SCA1, SCA2, SCA7, and MSA
  - Dentatorubral-pallidoluysian (DRPL) type for SCA1, SCA3, DRPL ataxia (DRPLA), and PSP

OTHER HIGH YIELD POINTS

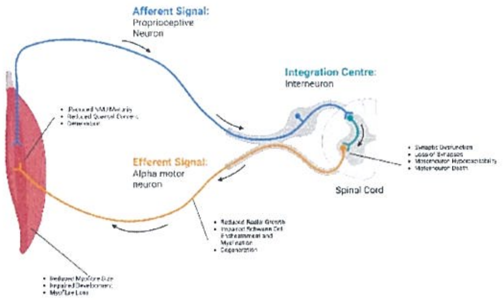
- Combination of clinical findings and lesion distribution was, historically, the gold standard for classifying SCDs
- After identification of genetic abnormalities, genotyping has replaced the conventional approach to diagnosis
- SCAs are a diverse group of rare and slowly progressive neurological diseases
  - There are currently 48 known subtypes
- Often inherited
  - **The majority exhibit autosomal dominant inheritance pattern**
  - The causative gene is unknown in 25-40% of cases, **CAG repeats** are found in SCA1, 2, 3, 6, 7, 8, 12, and 17
  - Other SCAs include repeats of larger nucleotide sequences
- Worldwide, SCA3 is the most common, followed by SCA2, then SCA6, and SCA7
- Can mimic Parkinson's disease clinically – Parkinsonism and pyramidal signs are common; degeneration can be found in the SN
- There are a few unique clinical features that may help distinguish subtypes
  - Myoclonus: SCA14
  - Chorea: SCA17 and SCA27
  - Visual impairment: SCA7
  - Tremor: SCA12, SCA15, and SCA27

Algorithm for differentiating spinocerebellar diseases (SCDs). Differentiating between hereditary spinocerebellar ataxias (SCAs: SCA1, SCA2, SCA3, SCA6,SCA7) and dentatorubral-pallidoluysian atrophy (DRPLA), progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) can be based on findings in the pontocerebellar system, spinocerebellar system, inferior olivary nucleus, cerebellar cortex, cerebral white matter (CWM), and spinal cord


Spinocerebellar Diseases
SCA1, SCA 2, SCA 3, SCA 6, SCA 7, DRPLA, MSA, PSP
Pure Cerebellar Type?
Yes
No
SCA 6
Olivopontocerebellar (OPC) type or Dentatorubal-pallidoluysian (DR&PL) type
DR&PL Type
OPC Type
SCA 1, SCA 3, DRPLA, PSP
Spinocerebellar Tract?
Cerebral White Matter?
SCA 2, SCA 7, MSA
Yes
No
Yes
No
SCA 1, SCA 3
Inferior Olivary Nucleus
DRPLA, PSP
Internal Globus Pallidus
MSA
Spinal Cord?
SCA 2, SCA 7
Yes
No
Yes
No
Yes
No
SCA 1
SCA 3
PSP
DRPLA
SCA 2
SCA 7

SPINAL MUSCULAR ATROPHY

SPINAL MUSCULAR ATROPHY PHYSIOLOGIC EFFECTS


Afferent Signal:
Proprioceptive Neuron
Integration Centre:
Interneuron
Reduced NMJ Maturity
Reduced Quantal Content
Denervation
Synaptic Dysfunction
Loss of Synapses
Motorneuron Hyperexcitability
Motorneuron Death
Efferent Signal:
Alpha motor neuron
Spinal Cord
Reduced Radial Growth
Impaired Schwann Cell Ensheathment and Myelination
Degeneration
Reduced Myofibre Size
Impaired Development
Myofibre Loss

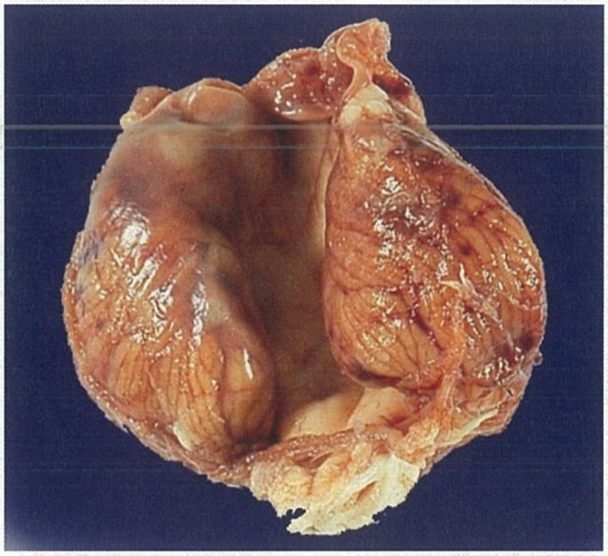
SPINAL MUSCULAR ATROPHY (SMA)

MORPHOLOGY

- Degeneration of motor neurons in the spinal cord
- Five subtypes – on a continuum from severe infantile to mild chronic disease
    - Type 0 (most severe): Neonatal onset
    - Type 1 (severe infantile form): Onset before 6 months of age; never sit independently
    - Type 2 (intermediate form): Onset during infancy, sit but never walk independently
    - Type 3 (myopathic form): Childhood onset; may cause loss of ambulation
    - Type 4 (mildest form): Adult onset with mild course

OTHER HIGH YIELD POINTS

- Progressive muscle weakness and respiratory insufficiency
- **Most common inherited neurodegenerative disorder**
- Autosomal recessive inheritance of survival motor neuron 1 ***(SMN1)* gene**
- Disease severity correlates with functional SMN protein levels produced by the copy gene ***SMN2***



CONGENITAL MALFORMATIONS AND RELATED DISORDERS

SADHNA AHUJA, MD
LAKSHMI RAMACHANDRAN NAIR, MD
RAQUEL T. YOKODA, MD

9. CONGENITAL MALFORMATIONS AND RELATED DISORDERS

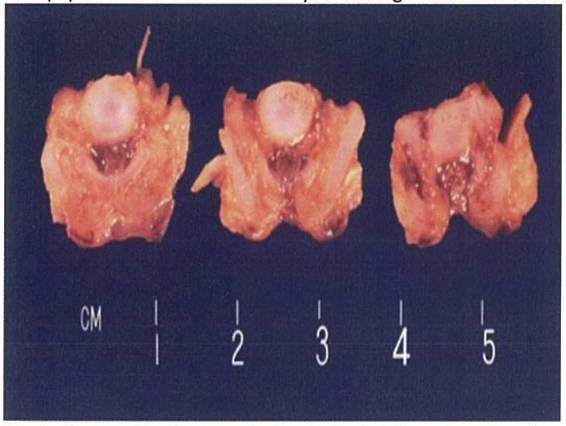
CONGENITAL MALFORMATIONS AND RELATED DISORDERS

TYPES OF CONGENITAL MALFORMATIONS AND RELATED DISORDERS	
NEURAL TUBE DEFECTS	NEURONAL MIGRATION DISORDERS
HIND BRAIN ABNORMALITIES	HIPPOCAMPAL SCLEROSIS
CEREBELLAR VERMIS MALFORMATIONS	CHROMOSOMAL NON-DISJUNCTION

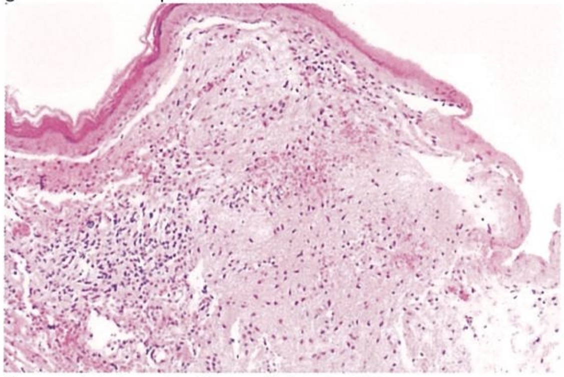
NEURAL TUBE DEFECTS

Types of neural tube defects	
Spinal cord defects	Spina bifida occulta Meningocele Myelomeningocele
Brain defects	Anencephaly Encephalocele
Both Brain and spinal cord	Craniorachischisis
Bony cranial vault defects	Exencephaly Acalvaria Agenesis of basioccipital bone

Autopsy sections from a case of myelomeningocele



Photomicrograph of myelomeningocele showing extension of glial tissue into superficial dermis



Pictures courtesy: Dr. George Kleinman, MD

GENERAL KEY FACTS

- Failure to close neural tube during development
- One of the most common malformations of the CNS
- Maternal serum AFP is measured through sandwich immunoassay and calculated through Multiples of the median (MoM)
- Most occur between 3rd to 4th week of gestational age as neural tube closure is completed around 27 weeks
- The exact incidence is not known and varies by country; the lowest in Asians
- The majority undergo spontaneous abortion
- Strong association with nutritional maternal folic acid deficiency
- Increase incidence with anti-epileptic drugs (valproic acid and carbamazepine)
- Folic acid supplementation has decreased the incidence of neural tube defects
- **"Lemon sign"** noted on antenatal imaging as scalloping/indentation of cerebral frontal lobes and generally associated with Chiari malformation
- **"Banana sign"** noted on antenatal imaging, posterior caudal displacement or abnormal shape of the cerebellum generally associated with hydrocephalus

SPINA BIFIDA

MORPHOLOGY

- Syringomyelia, hydromyelia, and diplomyelia may be present above the defect
- "Area medullovasculosa" contains un-organized neural tissue with congested blood vessels, disordered smooth muscle, and fat with atrophic cutaneous tissue

OTHER HIGH YIELD POINTS

- Can present with motor or sensory defects
- Lumbosacral teratoma is the most common differential (contains cartilage and dermal appendages)
- Spina bifida occulta type: asymptomatic patients and screening cannot be detected; hairy skin seen over the defect

SPINA BIFIDA CYSTICA

MORPHOLOGY

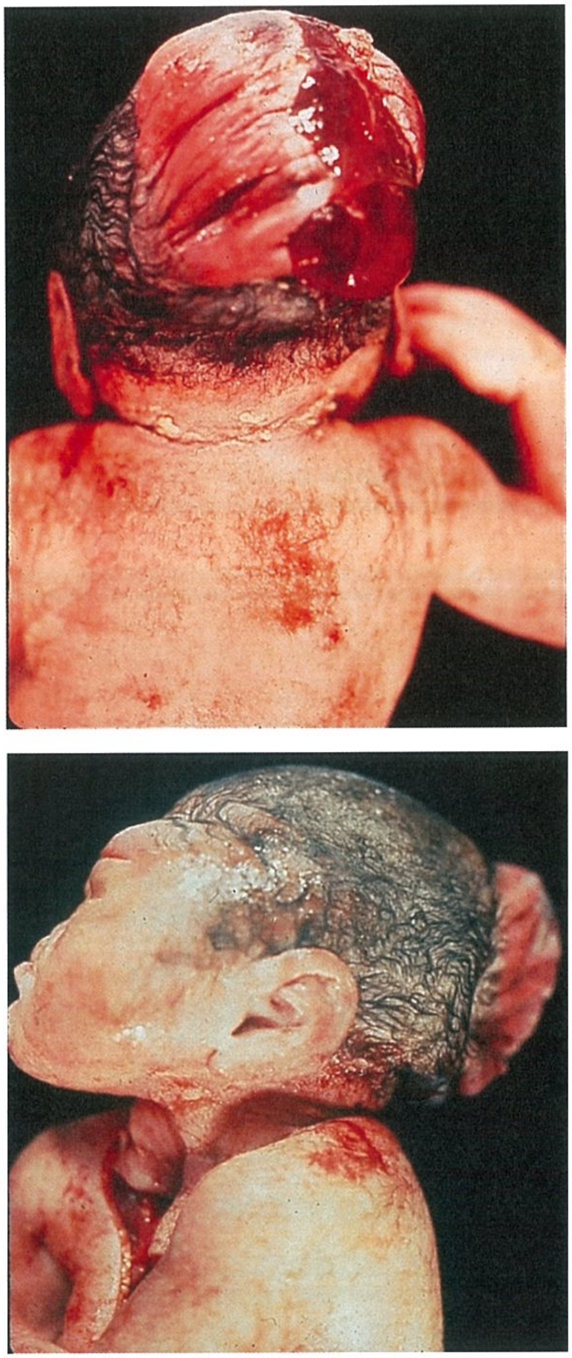
- Contains meningocele and myelomeningocele
- Meningocele: meninges protrude through vertebral defect
- Myelomeningocele: Meninges and malformed spinal cord protrude through the defect

OTHER HIGH YIELD POINTS

- Meningocele: generally normal development of the baby
- Myelomeningocele: Requires surgical repair, most frequent location lumbosacral> lumbar>thoracic regions
- Often associated with hydrocephalus and Chiari II malformations

9. CONGENITAL MALFORMATIONS AND RELATED DISORDERS

Gross picture of encephalocele showing protrusion of brain contents through skull defect



Pictures courtesy: Dr. George Kleinman, MD

TETHERED CORD SYNDROME (TSC)

- Traction of the conus medullaris pulled lower than the L2 vertebra
- It can be associated with other spinal cord malformations

ANENCEPHALY

MORPHOLOGY

- "Area cerebrovasculosa": **organized** vascular channels with **disorganized** neuroglial tissue with an increase in filtration of macrophages in the third layer with overlying atrophic cutaneous tissue
- Open cranial and cervical regions

OTHER HIGH YIELD POINTS

- Incompatible with life
- A major portion of central nervous tissue, skull vault, and scalp are absent

ENCEPHALOCELE

MORPHOLOGY

- **Protrusion of central nervous tissue and meninges through skull bony defects**
- Histology shows a variable amount of disorganized central nervous tissue, if large, may contain the cerebral hemisphere, ventricles, and choroid plexus
- Polymicrogyria and gray matter heterotopias are commonly associated

OTHER HIGH YIELD POINTS

- F>M, occipital regions>Frontal region
- Form of a Chiari III malformation
- CT (To observe bony defect) and MR (to observe contents) are important for diagnosis
- Disease of unknown etiology
- Syndromic associations have increased the incidence of recurrence
- Dandy-walker malformation
- Walker-Warburg syndrome
- Meckel-Gruber syndrome
    - ➢ AR, associated with mutations in 13 different genes
    - ➢ Generally, triad of occipital encephalocele, multicystic kidneys, and duct plate malformation of the liver

CRANIORACHISCHISIS

MORPHOLOGY

- Complete open neural tube with exposure of brain and spinal cord to amniotic fluid
- **Most severe form of neural tube closure**

EXENCEPHALY

MORPHOLOGY

- Brain tissue herniation out of the skull (anywhere frontal to occipital)

OTHER HIGH YIELD POINTS

- Amniotic bands can be associated with ischemic lesions in the brain, resulting in secondary exencephaly

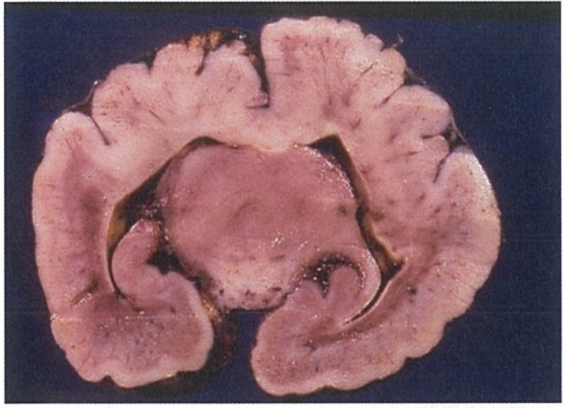
ACALVARIA

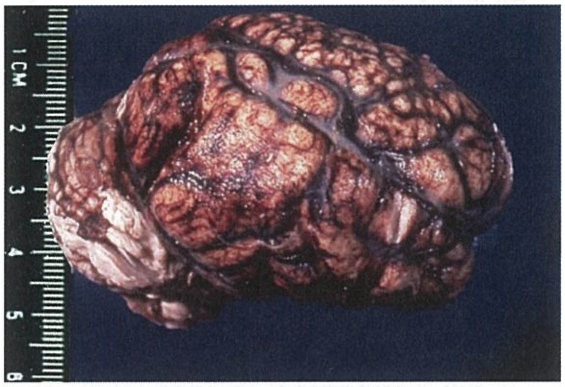
MORPHOLOGY

- **Absence of flat bones in the cranial vault**
- Can be complete or partial
- It can happen as part of the osteogenesis imperfect spectrum or as an isolated defect

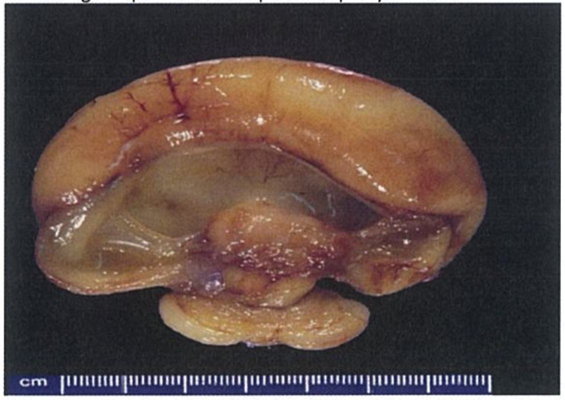
9. CONGENITAL MALFORMATIONS AND RELATED DISORDERS

Holoprosencephaly in the setting of trisomy 13 shows incomplete separation of two hemispheres

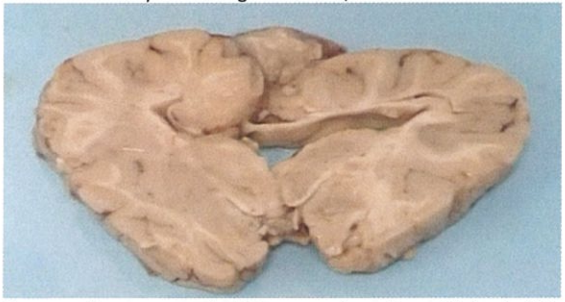




Another gross picture of holoprosencephaly



Coronal section showing agenesis of the corpus callosum
Pictures courtesy: Dr. George Kleinman, MD



Corpus callosum agenesis Picture courtesy: Raquel Yokoda, MD

HOLOPROCENCEPHALY

MORPHOLOGY

- **Defect in the rostral neural tube which causes incomplete separation of the two cerebral hemispheres**
- Histology: Spectrum of abnormalities ranging from cortical architectural abnormalities to heterotopias, generally cerebellum and brain stem are not affected. Olfactory nerves (bulb and tract) are absent - arhinencephaly
- Variants: Three main forms based on midline fissure are alobar, semilobar, and lobar forms
- **Alobar HPE**
  - Most common and most severe
  - Absent cerebral lobes, absent midline fissure, absent corpus callosum, septum pellucidum, and anterior commissure, fused basal ganglia, fused thalami with single banana shaped mono ventricle open rostrally
  - Facial abnormalities are common and include eye abnormalities: absent bilateral eyes, single eye (cyclopia), fused eyes, or eyes with narrow space are common, proboscis and cleft palate.
- **Semi lobar HPE**
  - Fused frontal lobes with interhemispheric fissure is only present in parietal-occipital region.
  - Facial abnormalities: Microphthalmia, anophthalmia, hypotelorism
- **Lobar HPE**
  - Fused frontal lobes with two separate lateral ventricles.
  - Facial anomalies: Depressed nose, cleft lip, closely spaced eyes
- **Middle interhemispheric variant of HPE/Syntelencephaly**
  - Separate anterior hemispheres but posterior frontal, parietal, thalami, and basal nuclei are fused
  - Facial anomalies: Depressed nose, cleft lip, small space between eyes
- **Arhinencephaly:**
  - Limited abnormalities: Generally, no olfactory bulbs present with no gyri recti

OTHER HIGH YIELD POINTS

- Sporadic is most common, but other associations, can be seen.
- Risk factors include maternal diabetes and alcohol usage
- Generally rudimentary olfactory and optic regions
- *Sonic Hedgehog (SHH)* gene on 7q36 is associated to the ventral forebrain malformations and craniofacial development
- Excess retinoic acid can inhibit SHH and is related to HPE

AGENESIS OF THE CORPUS CALLOSUM

MORPHOLOGY

- Corpus Callosum (CC) is completely form by 18-20 weeks
- Starting by 10 weeks, a glial bridge or massa commisuralis is formed between hemispheres, axons then cross it forming the CC
- Failure of bridge formation or failure of axons to cross it results if agenesis of the CC (ACC)
- It can be isolated or occur as a part of major syndromes (including trisomy 13 and 18)
- It can be complete or partial
- Clinically it is related to seizures or psychomotor delay

9. CONGENITAL MALFORMATIONS AND RELATED DISORDERS

HINDBRAIN ABNORMALITIES

KEY FEATURES

- Congenital structural defect in the hindbrain (cerebellum) with brain stem abnormalities
- They include Arnold Chiari malformation and Black pouch cyst

ARNOLD CHIARI MALFORMATION

MORPHOLOGY

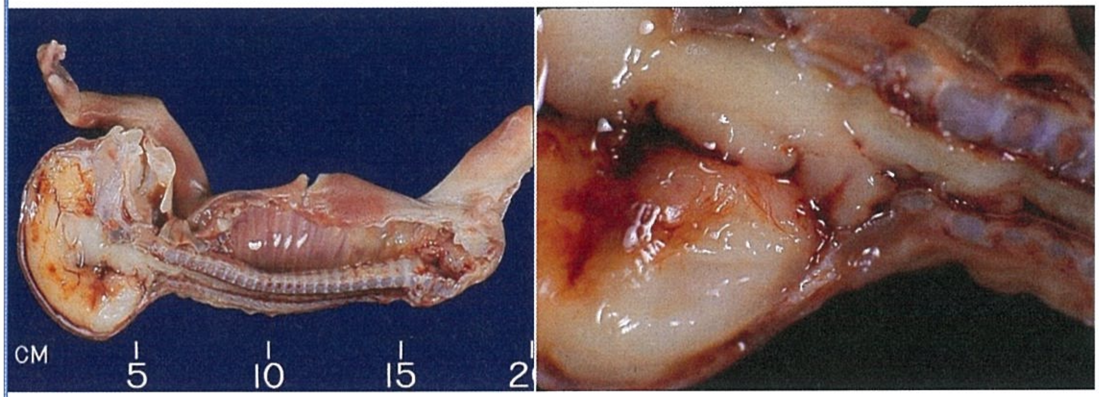
- Congenital structural defect involving the rhombencephalon and brain stem
- Are of 4 types
- **Chiari I malformation**
    - ➢ Posterior displacement of the cerebellar tonsils through foramen magnum
    - ➢ Young to middle aged patient
    - ➢ Skull abnormalities are common (up to 50%) and include small occiput, short clivus, narrow posterior fossa, empty sella, and accessory occipital condyle
    - ➢ Spine abnormalities are common and include scoliosis, thick ligamentum flavum, Klippel-feil deformity (cervical vertebral fusion), and odontoid process abnormalities
    - ➢ Spinal cord abnormalities include syrinx
- **Chiari II malformation**
    - ➢ Herniation of most posterior fossa contents (cerebellar vermis, brainstem and 4th ventricles)
    - ➢ Generally, presents in childhood
    - ➢ Hydrocephalus is commonly seen
    - ➢ Skull abnormalities include lacunar skull, lemon sign due to scalloping of the frontal bone, long stretched clivus, widely spaced foramen magnum
    - ➢ Spine abnormalities include Spina bifida, stretched cervical spine, odontoid process abnormalities, defective c1 posterior arch, Klippel-feil abnormalities
    - ➢ Ventricle abnormalities include hydrocephalus with un-equal ventricles, widening of the occipital horns, small 4th ventricle, and foramen of Magendie may be absent, short aqueduct
    - ➢ Meningeal abnormalities include abnormalities in tentorium cerebelli, falx cereberi may show fenestrations, arachnoid cyst, and thickening of the arachnoid
    - ➢ Usually there is a lumbosacral myelomeningocele
    - ➢ Brain abnormalities include absent septum pallucidum, absent cingulate gyrus, absent to rudimentary olfactory tracts/bulb and polygyria, adhesions in interthalamic regions, stretched mid brain Stretched pineal gland, abnormal cranial nerve nuclei, and medullary kink
- **Chiari III malformation**
    - ➢ Encephalocele of the occipital region, or high cervical
    - ➢ Other Intracranial abnormalities could be seen
- **Chiari IV malformation**
    - ➢ Hypoplastic cerebellum with no hindbrain herniation
    - ➢ Can be associated to pons hypoplasia

OTHER HIGH YIELD POINTS

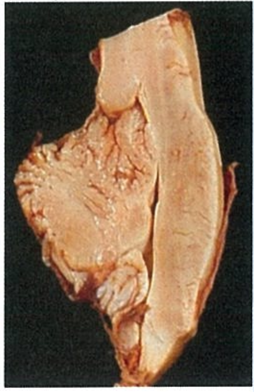
- F>M
- Common in Celtic descents
- Occasionally can be acquired
- Presentation
    - ➢ Generally young to middle aged patient
    - ➢ Variable symptoms, neck pain (MC), headache, balance issues, sensory loss in the shoulders and arms
    - ➢ Patients can be completely asymptomatic
    - ➢ Genetic disorders to which it may be associated with include achondroplasia, Klippel-fiel syndrome, Hadelu-cheney syndrome and Spondyloepiphyseal dysplasia tarda

Diagnosis- Radiological tests include Xray of the cervical spine, CT scan, MRI (imaging of choice), and an cardiac gated PC cine MRI for the CSF flow (for definite management)

Gross pictures of Arnold Chiari malformation



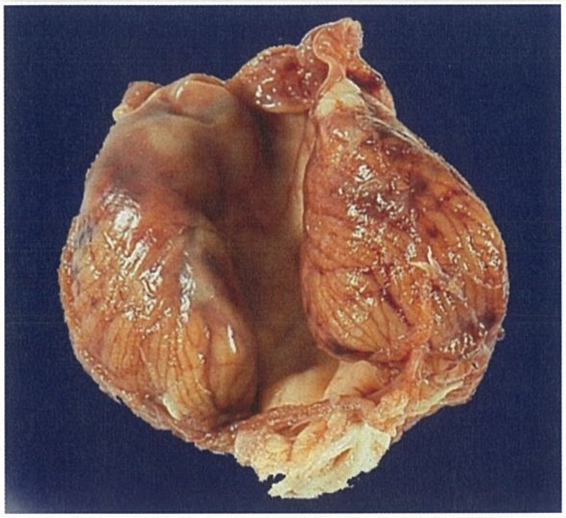
Cerebellar displacement through foramen magnum



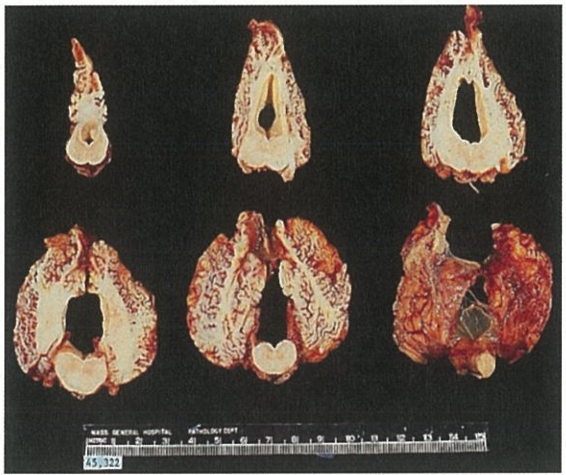
Picture courtesy: Dr.George Kleinman

9. CONGENITAL MALFORMATIONS AND RELATED DISORDERS

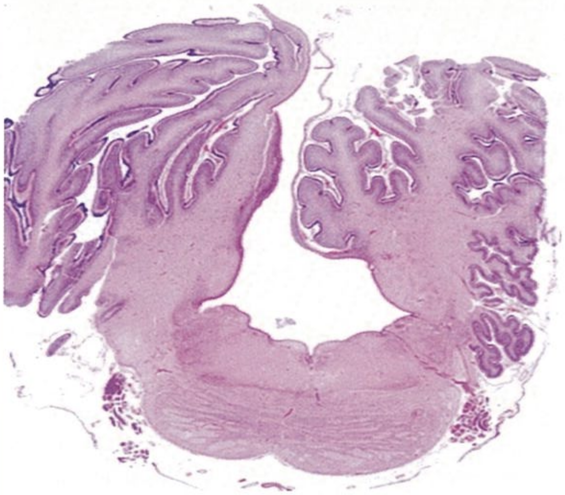
CEREBELLAR VERMIS MALFORMATIONS



Gross picture of Dandy walker malformation showing absence of cerebellar vermis and massive 4th ventricle



Another gross picture of Dandy Walker malformation



Photomicrograph showing dilated 4th ventricle
Pictures courtesy: Dr. George Kleinman

DANDY WALKER MALFORMATION

MORPHOLOGY

- Characterized by
  - Loss of cerebellar vermis
  - Large 4th ventricle
  - Wide posterior fossa
  - Elevated tentorium
  - Hydrocephalus
- Histology: Malformed neural tissue in the cerebellar vermis
- Dandy Walker Variant: Anteriorly placed vermis with variable hypoplasia, 4th ventricular enlargement may or may not be present
- Mega cisterna magna: large cisterna magna with absent cerebellar vermis abnormalities

OTHER HIGH YIELD POINTS

- The etiopathology is not known but abnormalities in the development of the 4th ventricle is the key known factor
- Partial trisomy in 13 q can be seen
- Vit A overdose is a risk factor
- Presentation
  - Generally in infancy, with enlarged head with increased circumference and motor deficits, vomiting
  - Breathing issues can be seen
  - Cardiac anomalies are commonly associated
- Imaging : X-ray for bony defects, enlarged fourth ventricle can be seen with MRI, CT, or Ultrasound
- Prognosis and Treatment: Depends on the severity of the disease.

JOUBERT SYNDROME

MORPHOLOGY

- Autosomal recessive disorder characterized by absent cerebellar vermis, enlarged superior cerebellar peduncles, with malformed midbrain
- Histology: White matter tract abnormalities, mainly at the cerebellar peduncles

OTHER HIGH YIELD POINTS

- Presentation
  - Hyponic child, with abnormal ocular movements
  - Breathing issues can be seen
  - Associations: encephalocele, liver fibrosis, endocrine problems, colobomas, accessory fingers, cleft lip or palate, retinitis pigmentosa
  - Multiple genetic mutations are associated
- Imaging: “**Molar tooth sign on MRI”:** Due to enlarged cerebellar peduncles and absent vermis

RHOMBENCEPHALOSYNAPSIS

MORPHOLOGY

- Rare disorder characterized by Absent cerebellar vermis with conjoined cerebellar cortices
- Histology: Fused dentate nucleus

OTHER HIGH YIELD POINTS

- Presentation
  - Hypotonic child with developmental delay
  - Associations: Polydactyly, septo-optic pituitary dysplasia
- Imaging : Small hindbrain with narrowing of aqueduct
- Prognosis and Treatment : Depends on the severity of the disease

9. CONGENITAL MALFORMATIONS AND RELATED DISORDERS

NEURONAL MIGRATION DISORDERS

Main Neuronal migration disorders
Lissencepahly
Schizencephaly and Porencephaly
Neuronal heterotopias
Polymicrogyria
Focal cortical dysplasia
Corpus callosum agenesis

Mutations associated with Lissencephaly Type 1	
ARX gene	Lissencephaly with abnormal genitalia and absent corpus callosum (X-linked)
XLIS gene or DCX gene (hindbrain is affected more than forebrain)	Males: Lissencephaly type 1 Females: Cortical heterotopias in periventricular and white matter regions
RELN gene (encodes reelin protein) (Hindbrain is affected more than forebrain)	Lissencephaly with abnormalities in cerebellum, (autosomal recessive)
LIS1 gene	Associations: Miller-Dieker syndrome Typical facial dysmorphia with Lissencephaly without gradient

Syndromes associated with Lissencephaly type 2 (Also known as Cerebro-Ocular dysplasia syndromes)	
Fukuyama congenital muscular dystrophy	Most common congenital muscular dystrophy in Japan, characterized by Polymicrogyria(one layered mostly) , with some areas of Lissencephaly, with microcephaly
Congenital muscular dystrophy types 1D and 1C	Similar findings of walker-Warburg syndrome plus myopathy and increase CK
Muscle eye brain disease	Milder version of muscular dystrophy syndrome
Walker-Warburg syndrome	Hydrocephalus, Lissencephaly retinal dysplasia with encephalocele. Severe, generally doesn't survive beyond infancy
CEDNIK syndrome	Cerebral dysgenesis, Neuropathy, Ichthyosis and keratoderma caused of loss of function mutations in SNAP29 which causes B1 integrin impairment

KEY FACTS

- Includes a spectrum of disease, which commonly share the same etiopathogenesis with disruptive migration of the neuroblasts during embryogenesis, but variable symptoms
- Early neural plate by 4 weeks is comprised of outer CRC layer (Cajal-Retzius cells) and inner subplate neurons
- CRC layer secretes matrix protein called reelin which directs neuroblasts in the cortical placement
- Radial glias are progenitor glia (from which can arise astrocytes, oligodendrocytes, and ependymal cells) and serve as guidance and allocation for developing neurons to eventually develop neocortex
- Gliogenesis follows neuro-genesis
- Neuroblasts migrate from germinal matrix to cortex
- Future cortical laminar architecture forms as inside to outside sequence (densely populated inner layers)
- In ~ thirty weeks, 6-layer cortico-laminar architecture can be appreciated
- Can be seen with chondrodysplasias like thanatophoric dwarfism and short rib polydactyly syndrome

LISSENCEPHALY

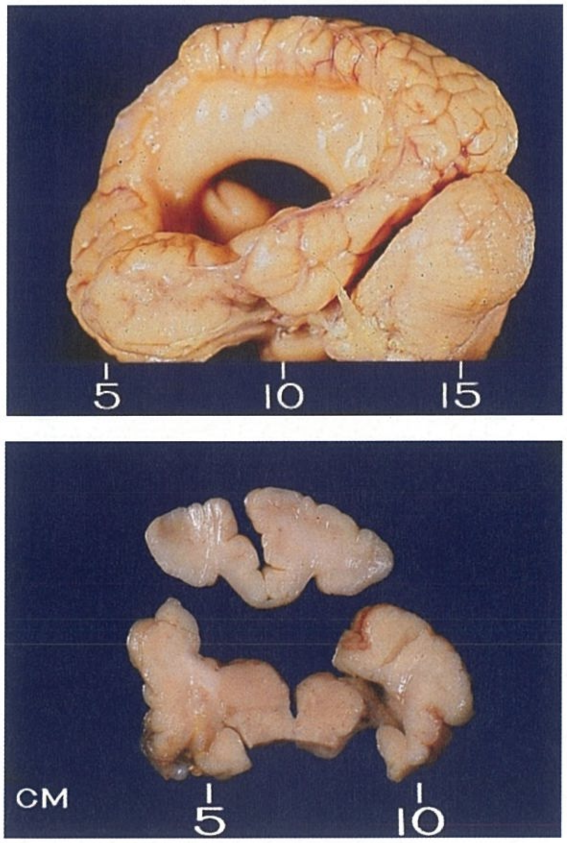
MORPHOLOGY

- Disorder of faulty neuroblast migration
- Gross: absence of cerebral convolutions with rudimentary sylvian fissure

OTHER HIGH YIELD POINTS

- Presentation: Variable from seizures, intellectual and developmental delays, feeding problems
- Radiology: Smooth brain with ventriculomegaly showing hourglass or "figure 8" appearance on axial imaging with sparse sulci with shallow Sylvian fissure
- Pachygyria: Focal abnormality mostly seen in metabolic disorders such as Zellweger syndrome, adrenoleukodystrophies, and glutaric aciduria IIA
- **Lissencephaly Type 1 "Smooth brain"**
  - Patterns and grades are important to distinguish different gene mutations and syndromes
  - **4 layer thick cortex instead of 6 layer cortex** (comprised of 1st molecular layer containing CRC, 2nd with disorganized pyramidal neurons, 3rd sparsely populated neuronal layer, 4th thick layer of disorganized pyramidal and granular neurons
  - 4 layer pattern is commonly seen LIS 1 gene
  - **"Double cortex" or Subcortical band heterotopia** (SBH): can be appreciated on imaging and gross and is a sandwich of cortex composed of overlying cortex with thick circumferential band of germinal matrix two of which are separated by thin layer of white matter- Most commonly seen with *XLIS* gene mutation
  - Hypoplastic cerebellum- commonly seen with *RELN* gene
  - Dysplastic inferior olives with dysplastic corticospinal tracts can be seen
  - **Miller-Dieker syndrome**: Syndrome of distinct facial abnormalities (include prominent forehead, bitemporal hollowing, midface hypoplasia, Small jaw, small nose with upturned nares, micrognathia and prominent upper lip) with Lissencephaly due to deletion in the short arm of chromosome 17 (LIS1 gene)

Types of Schizencephaly	
Type 1 "Closed Lip"	Type 2 "Open lip"
Cleft is present from ventricle to outer brain surface and is lined by heterotopic/polygyric grey matter	Cleft is present from ventricle to outer brain surface and is lined by heterotopic/polygyric grey matter
Cavum septum pellucidum present	Cavum septum pellucidum absent
Cleft has close lips with no CSF	Cleft has open lips with CSF
Generally isolated abnormality	Other lesions such as low lying fornices, heterotopias, and polymicrogyria, cortical defects may be present



Gross pictures of porencephaly
Picture credits: Dr. George Kleinman

- **Lissencephaly Type 2 "Cobblestone brain"**
  - Bumpy cortical surface with nodular grey-white junction
  - No cortical layers, but scramble of neurons and molecular layer
  - Disorder of overmigration of the neurons
  - Defective glycosylation in the post-translational processing of o-mannosylation defects
  - White matter is generally abnormal
  - Small cerebellum with or without polymicrogyria
  - Generally associated with ocular and muscle abnormalities
  - Dysplastic white matter tracts
  - Superficial heterotopias at the leptomeninges

SCHIZENCEPHALY

MORPHOLOGY

- Rare sporadic disorder with no sex predilection characterized by abnormal clefts that connects ependymal surface to pial surface
- Cleft lined by heterotopic gray matter
- Commonly two types, Type 1 (Closed lip) and Type 2 (Open lip)

OTHER HIGH YIELD POINTS

- Fetuses of young mother, with time of in utero-insults between 30-60 days of development
- CMV and other viral infections may be seen
- MCA territory commonly affected
- Can have association with septoptic dysplasia and optic atrophy

Differential diagnosis of Schizencephaly	
Differential diagnosis	Schizencephaly
Arachnoid cyst: CSF fluid cyst with mass effect with bulging of cranial bones. No ventricular communication, No cortical gray matter lining	Cortical grey matter which may have ventricular communication
Porencephaly: Extends from cortical surface to ventricular surface but it has gliotic white matter lining (Late in-utero insult after neuronal migration is complete)	Lined by heterotopic grey matter. Early in-Utero insult when neuronal migration is still ongoing
Focal cortical dysplasia: Cleft of cortical surface does not extend to ventricle	Cleft extends from pial to ventricular surface
Heterotopic gray matter: No ventricle cleft with nodular bulge of gray matter into the ventricles	Ventricular cleft present and no bulging seen

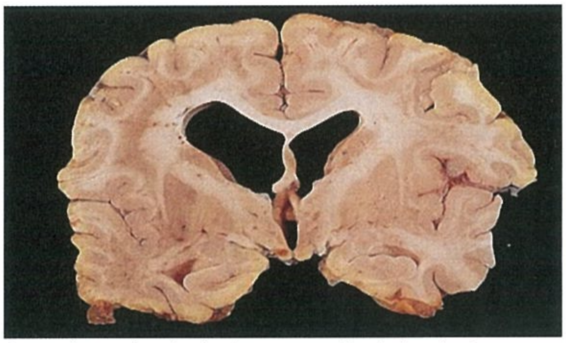
PORENCEPHALY

MORPHOLOGY

- Form of cysts/encephalomalacia composed of gliotic white matter that may extend from sub-pial to subependymal surface
- Cysts or cavities within the cerebral hemisphere
- Cysts result from encephaloclastic cause
- Generally symmetric and bilateral seen above sylvian fissure or central sulcus
- Septum pellucidum may be rudimentary
- Areas of polymicrogyria and nodular heterotopia can be seen

9. CONGENITAL MALFORMATIONS AND RELATED DISORDERS

Spectrum of Neuronal heterotopias and its associated conditions/malformations	
Sub-cortical band heterotopia (SBH)	Can be an isolated finding
Diffuse neuronal heterotopia	Common in epileptic patients May be early finding in myoclonic epilepsy
Periventricular nodular heterotopia	Bulge in the periventricular regions
Sub-ependymal heterotopia	Females of normal IQ with history of epilepsy X-linked dominant (Xq28 involving filamin gene) Lethal in males
Laminar heterotopias	Rare, mild disease, seen commonly in females with minimal IQ loss and epilepsy



Gross picture showing laminar grey matter heterotopia
Picture courtesy: Dr. George Kleinman

Etiopathologies associated with Polymicrogyria	
Aicardi syndrome	X-linked dominant
Metabolic disorders	Maple syrup urine disease Leigh syndrome Glutaric academia type 2 Pelizaeus-Merzbacher disease
Peroximal disorders	Adrenoleukodystrophy Zellweger syndrome
Acquired	TORCH infection In-utero vascular insults
Defects in OCLN gene in 5q region	AR also known as pseudo-TORCH syndrome characterized by polymicrogyria, microcephaly with linear band of calcification
Bilateral presylvian polymicrogyria	Seizures, motor skill disorders, mental retardation. Some cases due to mutation in SRPX2 gene (located on X chromosome)

OTHER HIGH YIELD POINTS

- Associated with mental retardation, congenital hemiplegia, epilepsy, and bilateral spasticity
- Bilateral porencephaly mimics schizencephaly radiologically and both terms can be synonymously used.

NEURONAL HETEROTOPIA

MORPHOLOGY

- Misplaced group of neurons due to interruption from germinal matrix to cortex
- Generally seen above or below the cortex
- Can be focal or diffuse

OTHER HIGH YIELD POINTS

- Generally seen with other CNS abnormalities except SBH which may occur as isolated finding

POLYMICROGYRIA (PMG)

MORPHOLOGY

- **Abnormal excessive undulations of the cerebral cortex separated by shallow enlarged sulci**
- Grossly thick cortex with excessive convolutions
- Cingulate or striate cortices are often not affected
- Histology: augmented folds with fused thin cortical layers (1 layer cortex with central blood vessel) but **4-layer cortex** can be seen

OTHER HIGH YIELD POINTS

- Most often as isolated finding
- Bilateral pre-sylvian polymicrogyria: most common form
- MCA territory commonly affected in acquired causes
- Some forms of PMG are due to prenatal hypoxic-ischemic insult, thus PMG is frequently seen within vascular territories (MCA)

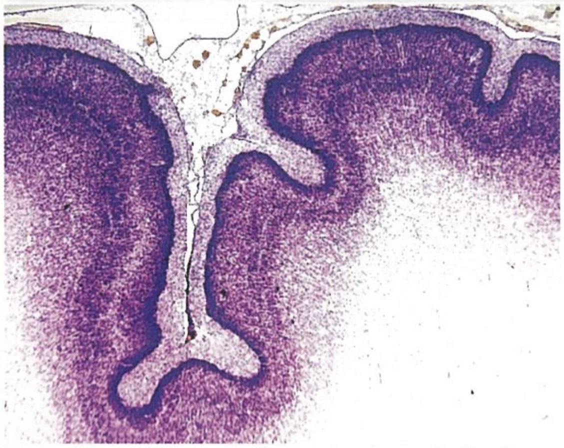
FOCAL CORTICAL DYSPLASIA

MORPHOLOGY

- Disorder of vertical columnar disorganization and tangential laminar disruption
- Gross: Agyria, pachygyria, polymicrogyria, neuronal heterotopias, cortical tubers can be seen
- **FCD type 1**: often more than one lobe (subtypes: 1a: abnormal vertical alignment of neurons; 1b abnormal horizontal alignment; 1c abnormal vertical and horizontal)
- **FCD type 2**: Frontal lobes most commonly involved. Atypical cells
- **FCD type 3**: Associated with other lesions (Hippocampal sclerosis, vascular malformations, etc.)

OTHER HIGH YEILD POINTS

- Most common cause of intractable epilepsy in children and third common cause of seizures in adults
- Most common surgical specimen of neuronal migration disorder encountered in neuropathology
- Etiologies still not known, studies shows some association with TSC1
- Variable clinical presentation from refractory seizures to developmental delay
- Symptoms generally improve after surgical removal of epileptogenic focus
- Radiology: **MRI shows blurred grey white junction with enhanced T2 signal intensity at subcortical region with or without gyral abnormalities**
- Two recognized classifications of focal cortical dysplasia, see tables



Photomicrograph demonstrating small gyri on cortical surface
Picture courtesy: Dr. George Kleinman

ILAE classification of Focal Cortical Dysplasia	
FCD I	Ia: aberrant radial cortical laminations Ib: Aberrant tangential cortical laminations Ic: Aberrant both tangential and radial laminations
FCD II	IIa: Dysmorphic neurons IIb: Dysmorphic and balloon neurons
FCD III	IIIa: Architectural abnormalities in temporal lobe with Hippocampal sclerosis IIIb: Architectural abnormalities with glial or glioneuronal neoplasm IIIc: Architectural abnormalities near vascular malformation IIId: cortical architectural abnormalities near any acquired incidents during infancy (vascular incidents, encephalitis)

- Suggested IHCs for FCDs are GFAP, NF, NeuN, myelin stain, and stains for associated tumors, if suspected

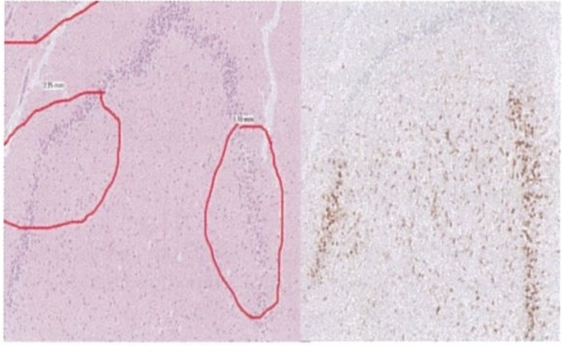
Palmini et al classification of Focal cortical dysplasia

Type	Key features
IA	Abnormalities in the architecture of the cortex, may have misplaced neurons in the white matter
IB	Abnormalities in the architecture of the cortex, may have misplaced neurons in the white matter plus immature or giant neurons. "**NOT DYSMORPHIC NEURONS**"
IIA	Abnormalities in the architecture of the cortex, with **DYSMORPHIC NEURONS**
IIB	Abnormalities in the architecture of the cortex, with **DYSMORPHIC NEURONS plus Balloon cells**

Key histological findings of FCD in different types	
FCD I Ia, Ib, Ic	Architectural abnormalities: Micro-columns of >8 neurons aligned vertically or loss of specified layer IB: Often missing distinctive layers 2 or 4 Immature neurons, giant neurons, heterotopic neurons in WM
FCD II	Architectural abnormalities: All layers affected except layer 1 **IIa**: Dysmorphic neurons, Immature neurons, giant neurons, heterotopic neurons in WM **IIb**: Dysmorphic and balloon neurons, Immature neurons, giant neurons, heterotopic neurons in WM, **white matter myelin abnormalities**
FCD III IIIa, IIIb, IIIc	Architectural abnormalities: variable from microcolumns, loss of specified layer to sclerosis Immature neurons, giant neurons, heterotopic neurons in WM

HIPPOCAMPAL SCLEROSIS

Neuronal loss marked on H&E and CD163 staining in Hipoccampal sclerosis in an infant due to recurrent hypoglycemia



Picture courtesy: Raquel Yokoda, MD

HIPPOCAMPAL SCLEROSIS – HS

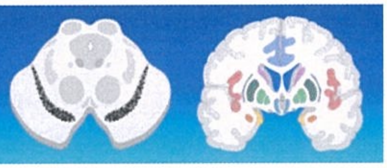
MORPHOLOGY

- High prevalence in a variety of congenital malformations
- ACC, HPE, Dandy-Walker complex, TSC, Fukuyama muscular dystrophy are associated with bilateral symmetric HS
- Polymicrogyria, schizencephaly, heteretopia – same sided abnormal hippocampal formation
- In patients with poroencephaly, HS is associated with intractable seizures
- Hippocampal neuronal loss can be the result of hypoxic-ischmic injury, hypoglycemia, toxins
- Aside from congenital settings, HS can be seen as a result of neurodegenerative disease, and mesial temporal lobe epilepsy.

OTHER HIGH YEILD POINTS

- Small asymmetric hippocampi can be seen in healthy relatives of temporal lobe epilepsy, representing a familial developmental variant of TLE with HS

9. CONGENITAL MALFORMATIONS AND RELATED DISORDERS



IN UTERO AND PERINATAL ISCHEMIA

Spectrum of in utero and perinatal ischemia
Hypoxic Ischemic Encephalopathy (HIE)
Periventricular Leukomalacia
Periventricular & Intraventricular Hemorrhage

Neuropathological sequalae in the HIE	
Term infant	Parasagittal injury Selective neuronal loss Spastic quadriparesis Cerebral palsy Status marmoratus
Preterm infant	Periventricular leukomalacia Spastic diplegia

Presentation of the PVL	
Focal PVL	**Non cystic**: Focal necrosis with glial scar may not be appreciated on imaging **Cystic:** Large areas of necrosis which develops multiple cystic lesions in the periventricular area, easily picked up by radiology
Diffuse PVL	Astrogliosis ad microgliosis Decrease in oligodendrocytes. Increase in oligodendrocyte progenitor cells Myelination defects Findings not clearly appreciated on imaging

Imamura et al grading system of PVL	
Grade 1	T2-weighted and fluid-attenuated recovery images show abnormally high signal intensity in periventricular white matter area, mostly bilateral in trigone areas of the lateral ventricles
Grade 2	Loss of periventricular white matter in abnormally high signal intensity areas with lateral ventricle enlargement
Grade 3	Diffuse and focal cystic changes in white matter

Ultrasound grading of the PVH	
Grade 1	Isolated periventricular hemorrhage
Grade 2	Periventricular hemorrhage plus intraventricular hemorrhage **but No Ventricular dilatation**

KEY FACTS

- Spectrum of diseases generally in premature infants or infants with prominent pathogenic mechanism, which is impaired cerebral blood flow

HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE)

MORPHOLOGY

- Characterized by encephalopathy due to the perinatal asphyxia (due to impaired cerebral blood flow)
- Gross findings: Cerebral swelling, blurred grey, white junction with dusky grey matter, infarcts in white matter
- Histology:
    - Depending on the location of brain involved and can follow the same hypoxic sequalae from red neurons to gliotic parenchyma
    - "Ulegaria" Atrophy of the deep cerebral sulci leading to mushroom like appearance of the sulci
    - Hippocampus: often spared in premature infants but there is selective vulnerability in the CA1 regions and Purkinje cells are prone to damage in the term infants
    - Status marmoratus: neuronal loss with abnormal myelination in the basal ganglia creating the "marbled" appearance
- Cellular damages may be reversible in early stages
- Extended perinatal hypoxia can lead to irreversible damage to neural tissue

OTHER HIGH YIELD POINTS

- Presentation
    - Depending on the gestational age of the baby and area of the brain involved and can range from hypertonic hyper alert infant to floppy baby with bradycardia
    - Status marmoratus: generally, presents with cerebral palsy
    - Polymicrogyria, schizencephaly, porencephaly seen be seen with HIE if vascular insults happen prenatally.
- Clinical staging systems include Sarnat and Sarnat staging
- Monitoring of vitals, blood sugar levels, ventilation support, and anti-epileptic therapy for seizures
- Cerebral hypothermia: slow the brain metabolism and injury. Better results with moderate HIE

PERIVENTRICULAR LEUCKOMALACIA (PVL)

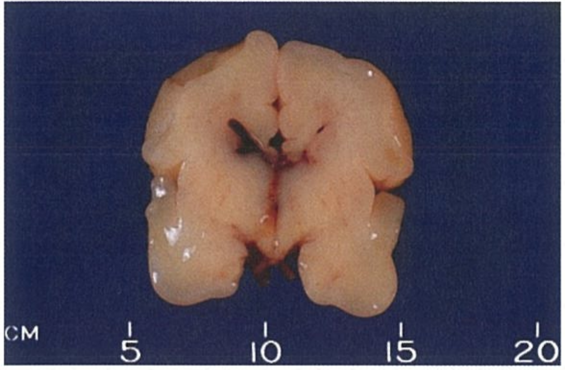
MORPHOLOGY

- White matter injury occurring during perinatal period due to impaired cerebral blood flow
- Gross findings: Softening of the peri-ventricular regions along lateral ventricles, at the level of foramen of Monro
- Cystic changes if advanced damage
- Histology
    - Coagulative necrosis ~24 hours, axonal spheroids, activated increase in microglia density, macrophage infiltration followed by necrosis lead to glial scar or cavitary formation
    - Mineralization at the cystic cavity may occur and can mimic fungal organisms
    - Perinatal telencephalic leukoencephalopathy: referred to diffuse white matter gliosis

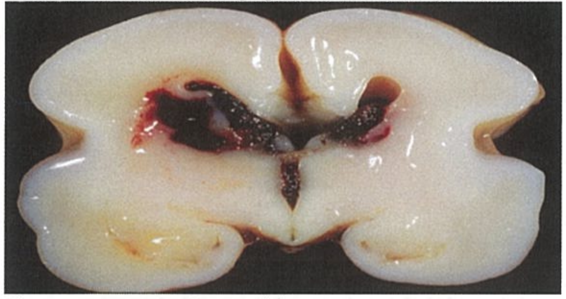
OTHER HIGH YIELD POINTS

Grade 3	Periventricular hemorrhage plus intraventricular hemorrhage **with Ventricular dilatation**
Grade 4	Periventricular hemorrhage plus intraventricular hemorrhage **with Ventricular dilatation**

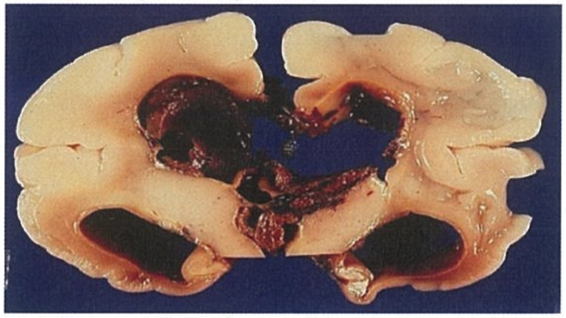
Germinal matrix hemorrhage grade 1, isolated ventricular bleed



Germinal matrix hemorrhage grade 2, no ventricular dilation



Picture courtesy: Dr. George Kleinman



Germinal matrix hemorrhage grade 3 with ventricular dilation

- Gestational age is the most important risk factor, the lower the gestational age, higher the risk for PVL
- Around 30% have associated PVH
- Size of the corpus callosum may be small
- Presentation can be focal or diffuse
- Spastic diplegia or spastic quadriplegia due to consequence of white matter damage (cystic PVL)
- Imaging and laboratory findings: Cranial ultrasound imaging (cUS): Non-invasive imaging modality used at bedside nursery and can detect focal lesions, cystic lesions which appear as echo densities along the subependymal lining and subcortical white matter
- MRI: Imamura et al grading system of PVL
- Prognosis and Treatment: Depends on the severity of the disease
- Supportive care

PERIVENTRICULAR AND INTRAVENTRICULAR BRAIN HEMORRHAGE (PVH/IVH)

MORPHOLOGY

- Hemorrhagic lesions around the ventricles during development
- Grossly PVH tends to involve more than one lobe
- Histology: Fresh bleeding in the germinal matrix, can split the ventricular lining and lead to IVH
- Areas of PVL can be seen

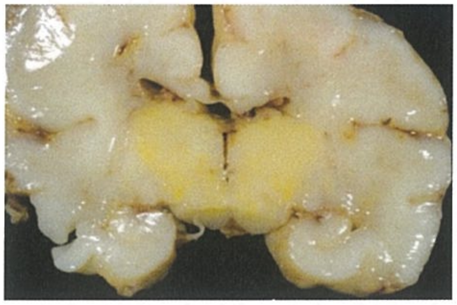
OTHER HIGH YIELD POINTS

- Age of the gestational age is most important factor; the chances are highest if the gestational age is less than 28 weeks
- Other risk factors include vitamin K deficiency, trauma, cocaine abuse and other rare congenital vascular malformations
- Large veins of the germinal matrix are most likely source of hemorrhage.
- VEGF overexpression in the cord blood may serve as indicator for feto-maternal hemorrhage-IVH risk
- Generally, presents in the first few days of birth (~48 hours)
- Semi-comatose baby with bulging fontanelle, may have seizures
- Higher the grade, higher are the long term neurological sequalae
- ~ 75% with periventricular hemorrhage with infarction can have spastic or quadriplegic cerebral palsy
- Steroids and Indomethacin shows decrease in severity of IVH
- Pancuronium bromide, muscle relaxant for paralysis and maintenance of cerebral blood flow

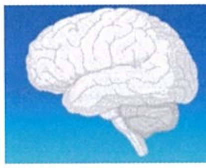
BILIRUBIN ENCEPHALOPATHY

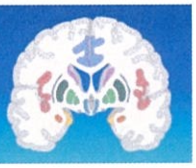
MORPHOLOGY

- Neurological syndrome due to deposition of bilirubin in the certain parts of the brains due to Increased plasma bilirubin concentration (>30 mg/dl in USA Cutt off, >25 mg/dl in Canada) in neonates which causes Bilirubin induced neurological dysfunctions (BIND)
- Bilirubin accumulated in the brain deep grey matter
- Gross findings: Symmetric yellow discoloration of the basal ganglia (globus pallidus, thalamus and locus cereus (thalami and LC mostly affected in premature neonates)
- Histology: Edematous neuropil with neuronal vacuolization, chromatolysis
- Bilirubin pigment may be only seen in frozen sections
- Bilirubin is neuro-toxic to developing neurons



Kernicterus- Diffuse yellowish discoloration of the cut surfaces





OTHER HIGH YIELD POINTS

- Presentation includes yellowing of skin, and conjunctiva
- **Acute encephalopathy**: variable muscle tones, lethargic, feeding problems, high pitched cry, spastic torticollis
- **Chronic encephalopathy:** movement disorders (athetosis), auditory neuropathy, nystagmus, strabismus, abnormalities in developing deciduous teeth
- **Subtle encephalopathy**: isolated auditory problems, learning problems, may have movement disorders
- **Kernicterus**: Chronic sequela of BIND with permanent neurological deficits
- Other permanent neurological sequela include permanent loss of hearing (Sensorineural hearing loss)
- Presentation may not be obvious in premature neonates, neonates with G6PD deficiency has increased risk
- Imaging and Lab Findings
    - ➢ Auditory brain stem evoked response: Able to detect auditory problems both reversible and non-reversible
    - ➢ Prominent T2 signal intensities in the basal ganglia nuclei (globus pallidus, putamen, thalami)
    - ➢ Lab Findings: Total serum/plasma bilirubin concentration: valuable marker to assess the risk for kernicterus in premature neonates
    - ➢ The degree of jaundice should not be estimated visually, mainly in infants with dark pigmentation
- Prognosis and Treatment : Babies born before 35 weeks may benefit from phototherapy and exchange transfusion based on the clinical risk assessment of developing permanent neurological sequala

Successful breastfeeding can decrease the risk

FETAL ALCOHOL SYNDROME (FAS)

MORPHOLOGY

- Non-genetic congenital abnormalities that occur due to consumption of alcohol during pregnancy
- FAS represents the severe end of fetal alcohol spectrum disorders.
- One of the common causes of mental retardation
- Grossly **Distinct facial features include** Epicanthal folds, short palpebral fissures, midface hypoplasia, thin and smooth philtrum, upturned nose
- Midline structural defects can be seen
- Bony and cardiac anomalies and small metatarsal or metacarpal bones can be seen
- Histology depends on the structural defects

OTHER HIGH YIELD POINTS

- Pathophysiology: Alcohol from mother blood stream crosses the placenta and enters into developing brain of the fetus and impairs the ability of the fetal brain to receive sufficient nutrients.
    - ➢ First trimester alcohol manifestations: Alcohol hinders with neuronal migration of cells
    - ➢ 2nd trimester alcohol manifestations has severe clinical features if its extreme amounts of alcohol consumption from 10th to 20th week.
    - ➢ 3rd trimester alcohol manifestations: Hippocampus is affected the most
- Presentation includes cognitive, sleep and behavioral issues
- Impaired growth, impaired language development
- Inappropriate sexual behaviors and academic legging
- Imaging: Brain defects such as agenesis of corpus callosum, misplaced angled corpus callosum, lissencephaly, holoprosencephaly or cystic hygroma can be seen
- No specific treatment, heart anomalies may require surgery
- Parenteral counseling may help

Diagnostic criteria for FAS (all must be met)
Short palpebral fissures, midface hypoplasia, thin and smooth philtrum
Growth retardation (Prenatal or Postnatal height and weight <10th percentile
Structural neurological or functional impairment
History of alcohol exposure confirmed or unknown

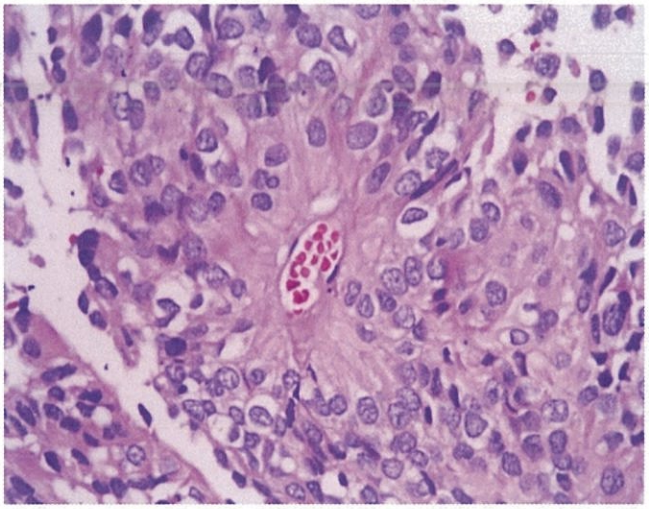
9. CONGENITAL MALFORMATIONS AND RELATED DISORDERS

CHROMOSOMAL NON-DISJUNCTION

KEY FACTS

- The most common cause is maternal meiotic non-disjunction
- Lead to developmental neurological, cardiac, and other anomalies
- Common causes of first trimester pregnancy losses (mainly trisomy 16)
- Increase risk with advanced maternal age
- Ancillary tests: Non-invasive maternal testing: high negative predictive value with low specificity, positive testing will follow invasive testing such as amniocentesis and cytogenetic studies include FISH, Karyotype and microarray
- Ultrasound for structural neurological and cardiac defects

Trisomy 13 Generally, die with first year of life CNS defects: - Holoprosencephaly - Agenesis of corpus callosum - spina bifida	**Non-CNS abnormalities:** **- Midline defects, cleftal defects of lip and palate** **- Post-axial polydactyly** **- Rocker bottom feet** **- Clenched fist** **- Cardiac anomalies include ASD, VSD, or dextrocardia** **- IUGR**
Trisomy 18 Generally, die within first year of life CNS defects: - spina bifida	Non-CNS abnormalities: - Omphalocele - Radial aplasia - Club foot - Facial features include micrognathia, low lying ears and hypotelorism
Trisomy 21 Life expectancy of 50-55 years CNS defects: - Dementia, early	Non-CNS abnormalities - Flat occiput - Macroglossia - Epicanthal folds - White spots on iris (Brushfield spots) - Rocker bottom feet - ASD, VSD, or ventricular canal defects - Duodenal atresia - Increase risk of AML



GLIAL TUMORS

SILVIA J. HERNANDEZ, MD

TUMORES GLIALES

Difusos

- → Adultos
  - Ⓐ Glioblastoma
    - Epiteloide
    - Celulas gigantes
    - Componente neuronal Primitivo
    - Gliosarcoma
    - Celulas pequeñas
    - Celulas granulares
    - Gemistocitos
    - Metaplasia epitelial
    - Moleculares
  - Ⓑ Astrocitoma (IDH Mutante)
    2°, 3°, 4°
  - Ⓒ Oligodendroglioma
    2°, 3°
- → Pediatricos
  - * Bajo Grado
    - Ⓐ Astrocitoma difuso
    - Ⓑ Glioma angiocentrico
    - Ⓒ Neuroepitelial polimorfo
    - Ⓓ Glioma difuso (MAPK alterado)
  - * Alto Grado
    - Ⓐ Glioma difuso de linea media
    - Ⓑ Glioma Hemisferico difuso
    - Ⓒ Glioma difuso pediatrico de alto grado (3 subtipos)
    - Ⓓ Glioma Hemisferico infantil (4 subtipos)

Circunscritos

- Ⓐ Astrocitoma
  - Pilocitico
  - Pilomixoide
- Ⓑ Astrocitoma de alto grado c/caracteristicas piloides
- Ⓒ Xanto astrocitoma pleomorfico (2°, 3°)
- Ⓓ SEGA
- Ⓔ Glioma cordoide
- Ⓕ Astroblastoma
- Ⓖ Ependimomas
  - → Supratentorial
    - → ZFTA
    - → YAP 1
  - → Infratentorial
    - → Grupo A
    - → Grupo B
  - → Espinal
  - → Maxilopapilar
- Ⓗ Subependimoma.

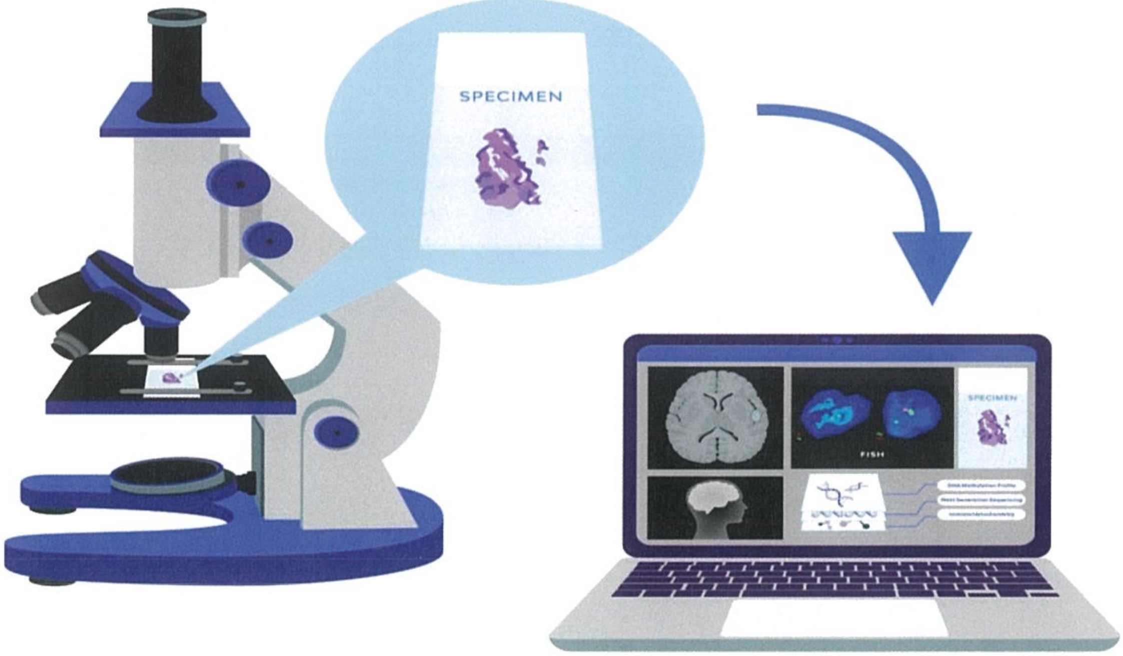
10. GLIAL TUMORS

CENTRAL NERVOUS SYSTEM TUMORS

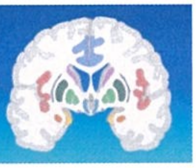
CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMORS (GENERAL CONSIDERATIONS)

- Tumors are classified using the World Health Organization (WHO) system
- CNS WHO "Blue Book" 5th edition 2021, which follows:
  - The Human Genome Organization (HUGO) Gene Nomenclature Committee (HGNC) system for gene symbols and gene names
  - The Human Genome Variation Society (HGVS) for sequence variants
  - The International System for Human Cytogenetic Nomenclature (ISN) 2020 reporting guidelines for chromosomal alterations
  - International Society of Neuropathology – Haarlem consensus guidelines
  - International collaboration on cancer reporting

- The **WHO classification** scheme uses an **integrated and layered** (tiered) diagnosis based on:
  - **Tumor site**
  - **Histopathologic classification** (types and subtypes)
  - **Biologic grade 1-4** (rendered in **Arabic numbers**) (refers to the natural behavior of the tumor without treatment)
  - **Molecular (genetic) findings**; if no molecular workup is available, the designation **"not otherwise specified (NOS)"** should be rendered nonetheless; if a molecular workup is available but the results do not render an accurate match between clinical, histologic, immunohistochemical, and/or genetic features the designation **"not elsewhere classified (NEC)"** may be specified



Schematic view of the new WHO integrated and layered diagnosis using histopathology grade, tumor site, and ancillary studies such as immunohistochemistry, FISH, next-generation sequencing, and DNA methylation profile



EXAMPLE 1	LAYERED REPORT STRUCTURE
Tumor Site	**Cerebrum (Frontal Lobe)**
Integrated Diagnosis	Oligodendroglioma, IDH-mutant and 1p19q-codeleted
Histopathologic Classification	Oligodendroglioma
CNS WHO Grade	2
Molecular Information	DNA methylation profile of oligodendroglioma, IDH-mutant and 1p19q-codeleted

EXAMPLE 2	LAYERED REPORT STRUCTURE
Tumor Site	**Cerebrum (Frontal Lobe)**
Integrated Diagnosis	Oligodendroglioma, NOS
Histopathologic Classification	Oligodendroglioma
CNS WHO Grade	2
Molecular Information	FISH and methylation studies unavailable

EXAMPLE 3	LAYERED REPORT STRUCTURE
Tumor Site	**Brainstem**
Integrated Diagnosis	Diffuse midline glioma, H3 K27-altered Subtype H3.3 K27-mutant
Histopathologic Classification	Diffuse midline glioma
CNS WHO Grade	4
Molecular Information	Methylation profile for H3 p.K28M (K27M) mutation

EXAMPLE 4	LAYERED REPORT STRUCTURE
Tumor Site	**Cerebrum (Frontal Lobe)**
Integrated Diagnosis	Astrocytoma, IDH-mutant
Histopathologic Classification	Astrocytoma
CNS WHO Grade	4
Molecular Information	IDH-1 mutation; CDKN2A/CDKN2B homozygous deletion

EXAMPLE 5	LAYERED REPORT STRUCTURE
Tumor Site	**Cerebellum**
Integrated Diagnosis	Pilocytic astrocytoma, KIAA1549::BRAF fusion
Histopathologic Classification	Pilocytic astrocytoma
CNS WHO Grade	1
Molecular Information	MAPK pathway gene alteration (KIAA1549::BRAF gene fusion)

EXAMPLE 6	LAYERED REPORT STRUCTURE
Tumor Site	**Cerebrum**
Integrated Diagnosis	Supratentorial ependymoma, NOS
Histopathologic Classification	Ependymoma
CNS WHO Grade	3
Molecular Information	FISH and methylation studies unavailable

WHO Classification of primary CNS tumours

Gliomas, Glioneuronal Tumours & Neuronal Tumours

Adult-type diffuse gliomas
- Astrocytoma, IDH-mutant
- Oligodendroglioma, IDH-mutant and 1p/19q-coldeleted
- Glioblastoma, IDH-wildtype

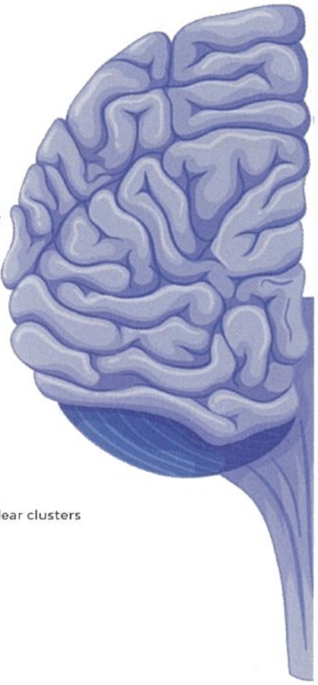
Paediatric-type diffuse low-grade gliomas
- Diffuse astrocytoma, MYB- or MYBL1-altered
- Angiocentric glioma
- Polymorphous low-grade neuroepithelial tumour of the young
- Diffuse low-grade glioma, MAPK pathway-altered

Paediatric-type diffuse high-grade gliomas
- Diffuse medline glioma, H3K27-altered
- Diffuse hemispheric glioma, H3G34-mutant
- Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- Infant-type hemispheric glioma

Circumscribed astrocytic gliomas
- Pilocytic astrocytoma
- High-grade astrocytoma with piloid features
- Pleomorphic xanthoastrocytoma
- Subependymal giant cell astrocytoma
- Chordoid glioma
- Astroblastoma, MN1-altered

Glioneural and neuronal tumours
- Ganglioglioma
- Gangliocytoma
- Desmoplastic infantile ganglioglioma / desmoplastic infantile astrocytoma
- Dysembryoplastic neuroepithelial tumour
- Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters
- Papillary glioneuronal tumour
- Rosette-forming glioneuronal tumour
- Myxoid glioneuronal tumour
- Diffuse leptomeningeal glioneuronal tumour
- Multinodular and vacuolating neuronal tumour
- Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
- Central neurocytoma
- Extraventricular neurocytoma
- Cerebellar liponeurocytoma

Ependymal tumours
- Supratentorial ependymoma
- Supratentorial ependymoma, ZFTA fusion-positive
- Supratentorial ependymoma, YAP1 fusion-positive
- Posterior fossa ependymoma
- Posterior fossa group A (PFA) ependymoma
- Posterior fossa group B (PFB) ependymoma
- Spinal ependymoma
- Spinal ependymoma, MYCN-amplified
- Myxopapillary ependymoma
- Subependymoma



Choroid Plexus Tumours

- Choroid plexus papilloma
- Atypical choroid plexus papilloma
- Choroid plexus carcinoma

Pineal Tumours

- Pineocytoma
- Pineal parenchymal tumour of intermediate differentiation
- Pineoblastoma
- Papillary tumour of the pineal region
- Desmoplastic myxoid tumour of the pineal region, SMARCB1-mutant

Cranial & Spinal Nerve Tumours

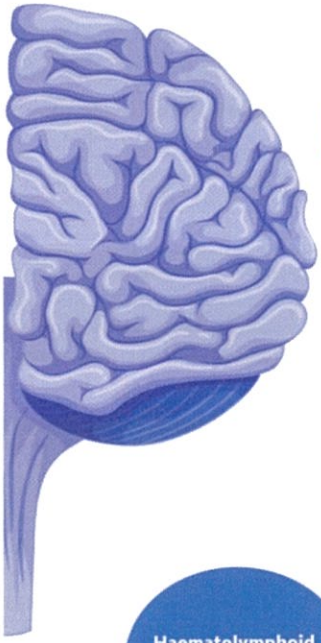
- Schwannoma
- Neurofibroma
- Perineurioma
- Hybrid nerve sheath tumours
- Malignant melanotic nerve sheath tumour
- Malignant peripheral nerve sheath tumour
- Cauda equina neuroendocrine tumour (previously paraganglioma)

Embryonal Tumours

Medulloblastomas, moleculary defined
- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and TP53-wildtype
- Medulloblastoma, SHH-activated and TP53-mutant
- Medulloblastoma, non-WNT/non-SHH

Medulloblastomas, histologically defined
- Medulloblastoma

Other CNS embryonal tumours
- Atypical teratoid/rhabdoid tumour
- Cribriform neuroepithelial tumour
- Embryonal tumour with multilayered rosettes
- CNS neuroblastoma, FOXR2-activated
- CNS tumour with BCOR internal tandem duplication
- CNS embryonal tumour, NEC/NOS



Other Mesenchymal Tumours Involving the CNS

Fibroblastic and myofibroblastic tumours
- Solitary fibrous tumour

Vascular tumours
- Haemangiomas and vascular malformations
- Haemangioblastoma

Skeletal muscle tumours
- Rhabdomyosarcomas

Tumours of uncertain differentiation
- Intracranial mesenchymal tumour, FET::CREB fusion-positive
- CIC-rearranged sarcoma
- Primary intracranial sarcoma, DICER1-mutant
- Ewing sarcoma

Chondrogenic tumours
- Mesenchymal chondrosarcoma
- Chondrosarcoma
- Dedifferentiated chondrosarcoma

Notochordal tumours
- Chordoma

Melanocytic Tumours

Diffuse meningeal melanocytic neoplasms
- Melanocytosis and melanomatosis

Circumscribed meningeal melanocytic neoplasms
- Melanocytoma and melanoma

Haematolymphoid Tumours Involving the CNS

Lymphomas
- Primary diffuse large B-cell lymphoma of the CNS
- Immunodeficiendy-associated CNS lymphomas
- Lymphomatoid granulomatosis
- Intravascular large B-cell lymphoma
- MALT lymphoma of the dura
- Other low-grade B-cell lymphomas of the CNS
- Anaplastic large cell lymphona (ALK+/ALK-)
- T-cell and NK/T-cell lymphoma

Histiocytic tumours
- Erdheim-Chester disease
- Rosai-Dorfman disease
- Juvenile xanthogranuloma
- Langerhans cell histiocytosis
- Histiocytic sarcoma

Germ Cell Tumours

- Germ cell tumours of the CNS
- Teratoma (mature and immature)
- Germinoma
- Yolk sac tumour
- Embryonal Carcinoma
- Choriocarcinoma
- Mixed germ cell tumour

Tumour of the Sellar Region

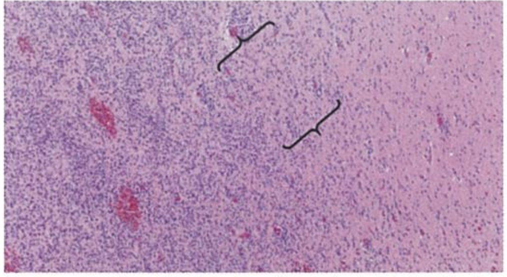
- Adamantinomatous craniopharyngioma
- Papillary craniopharyngioma
- Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocytoma
- Pituitary adenoma / pituitary neuroendocrine tumour
- Pituitary blastoma

Meningioma

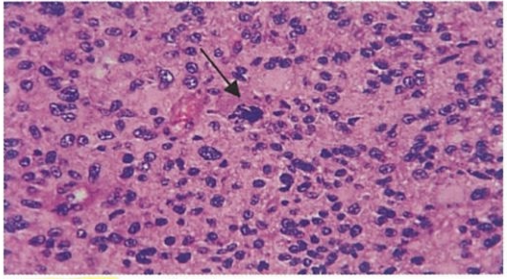
- Meningioma

ADULT-TYPE DIFFUSE GLIOMAS

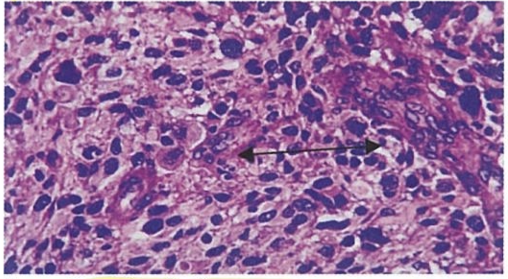
Infiltrative growth pattern with no margins



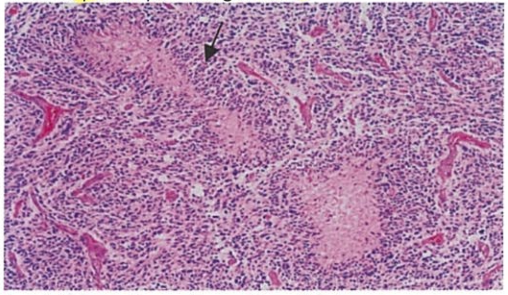
Numerous cells with pleomorphism, atypia, and mitosis



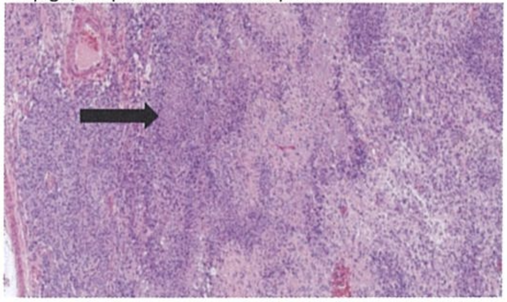
Microvascular proliferation



Areas of pseudopalisading necrosis



Serpiginous pattern of necrotic palisades



GLIOBLASTOMA, IDH-WILDTYPE (CNS WHO GRADE 4)

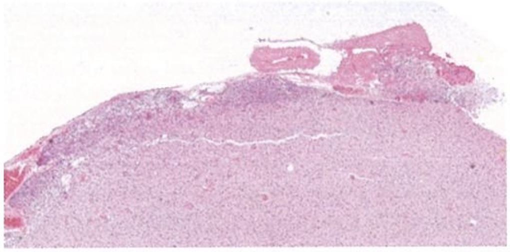
MORPHOLOGY

- **Diffusely infiltrating** astrocytic neoplasm, composed of high cellularity, nuclear atypia, brisk mitotic activity, and **at least one** of the following:
  - Microvascular proliferation
  - Pseudopalisading necrosis
  - Polysomy 7 and monosomy 10 (+7/-10)
  - EGFR gene amplification
  - TERT promoter mutation
- Other features: Highly heterogeneous morphology with poorly differentiated, fusiform, round, pleomorphic, small, lipidized, granular, and/or epithelioid cells
- Secondary structures of Scherer (indicative of infiltrative growth):
  - Subpial spread
  - Perineuronal satellitosis
  - Perivascular accumulation
  - Growth along white matter tracts
- **Specific morphologic subtypes:**
  - **Epithelioid glioblastoma** – associated with BRAF mutations Ⓐ
  - **Giant cell glioblastoma** – TP53 mutations common Ⓑ
  - **Glioblastoma with primitive neuronal component** Ⓒ
  - **Gliosarcoma** – GFAP-negative sarcomatous component Ⓓ
- **Specific morphologic patterns:**
  - Small cell glioblastoma Ⓔ
  - Granular cell glioblastoma Ⓑ Ⓕ
  - Lipidized glioblastoma
  - Glioblastoma with gemistocytes Ⓖ
  - Glioblastoma with oligodendrocyte-like cells
  - Glioblastoma with epithelial metaplasia (squamous or adenomatous) Ⓗ
- **Gross exam**: Whitish-gray, fleshy, ill-defined lesion with necrotic areas; thrombosed **"black veins"** are highly characteristic of cortical infiltration; infiltration to the meninges results in induration; necrotic, symmetric lesions bridging the corpus callosum

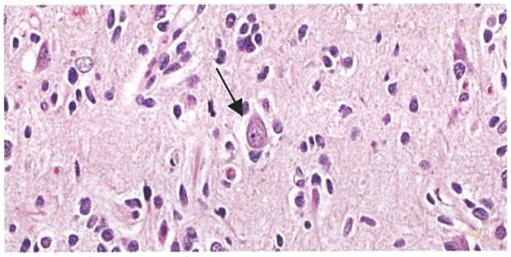
OTHER HIGH YIELD POINTS

- Clinically, depending on location, may present with focal neurologic defects such as aphasia or hemiparesis and/or seizures, headaches, nausea, or vomiting
- Affects all cerebral lobes and is most commonly located in subcortical white matter and deep gray matter; may extend through the corpus callosum into the contralateral hemisphere; may also affect brainstem, cerebellum, and spinal cord
- **Most common** primary CNS malignancy **in adults**
- Typically occurs in **older (> 55 years old)** adults
- On imaging, irregularly shaped with ring-shaped enhancement; it can grow along the corpus callosum into the other hemisphere (**"butterfly glioma"**)
- Treatment includes gross total resection followed by radiation and alkylating chemotherapy
- MGMT promoter methylation predicts responsiveness to alkylating and methylating chemotherapy agents (i.e., temozolomide)
- Poor prognosis, median overall survival ~15 months
- IHC:
  - Glial markers: (+) GFAP, OLIG2
  - (-) IDH1 R132H, H3K27M, H3 G34R; ATRX (retained), H3K27me3 (retained)
  - Ki-67 proliferation index is > 15-20%

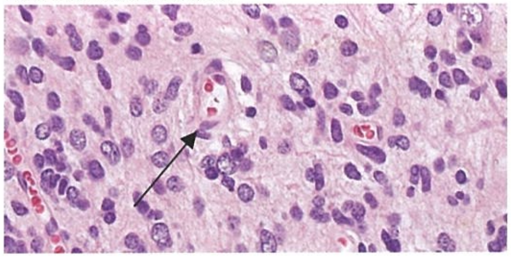
Secondary structures with subpial spread

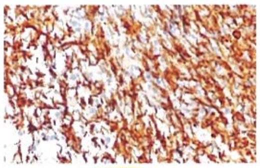


Perineuronal satellitosis

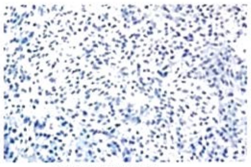


Perivascular accumulation

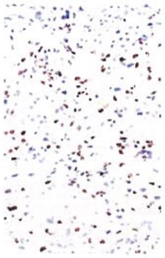




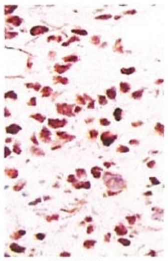
GFAP



IDH1 R132H



p53



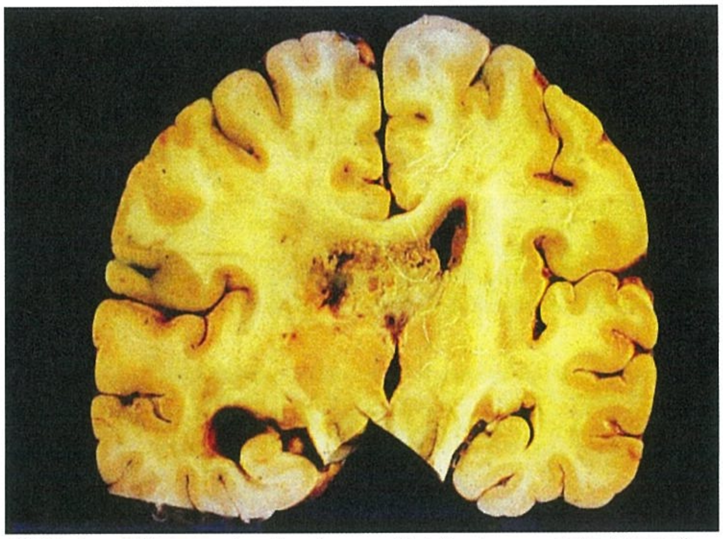
ATRX

Ki-67

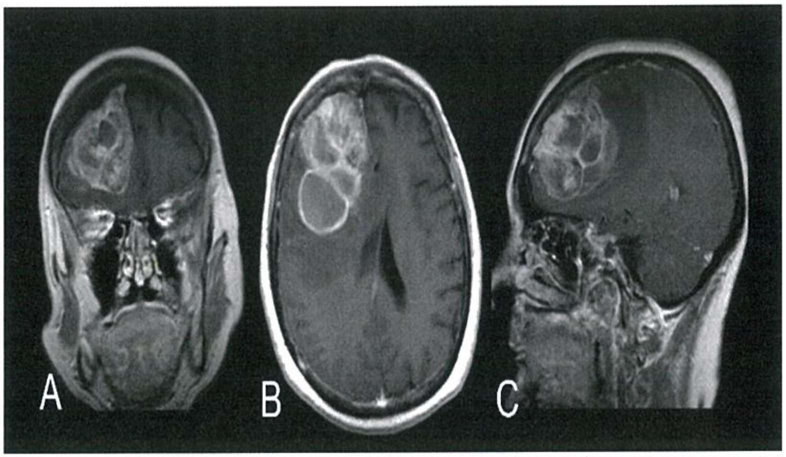
Path Presenter

Path Presenter

- Molecular: **IDH1/IDH2 (-); TERT promoter mutation**; **EGFR** gene amplification or combined **whole chromosome 7 gain and whole chromosome 10 loss**
(+7/-10); alterations of RTK genes, PI3K pathway genes, and PTEN in up to 90%; CDKN2A/CDKN2B deletion; BRAF V600E (epithelioid GB in 50%); MYC or **MYCN** amplification (neuronal component); radiation-induced gliomas PDGFRA, TP53, CDKN2A deletion; gene fusions of the receptor tyrosine kinase (RTK) family (EGFR, FGFR3, MET, NTRK1/NTRK2/NTRK3, PDGFRA**)**



Glioblastoma. The coronal section shows an ill-defined, gray-whitish mass with necrotic areas and focal hemorrhage
Picture courtesy: Edmundo Castelan, MD

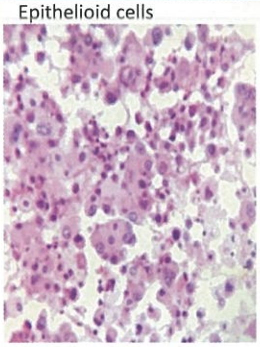


Glioblastoma. A. Coronal, B. Axial, and C. Sagittal images of ring-enhancing tumor on T1-weighted MRI show a ring or rimmed area of contrast enhancement that circumscribes tumor necrosis with peritumoral edema

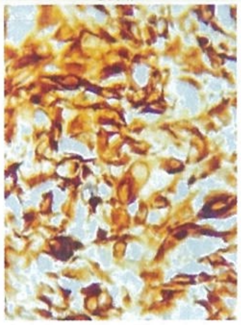
Path Presenter

Path Presenter

Epithelioid cells



GFAP



EPITHELIOID GLIOBLASTOMA (CNS WHO GRADE 4)

1A

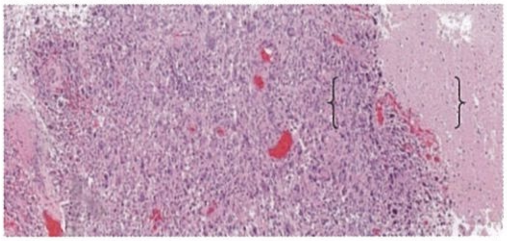
MORPHOLOGY

- Histologic subtype of glioblastoma, IDH-wildtype
- Composed of large eosinophilic cells with a prominent nucleolus
- Other features: Cells with more eccentric nuclei (similar to rhabdoid cells)
- Gross exam: Well-circumscribed, firm lesions

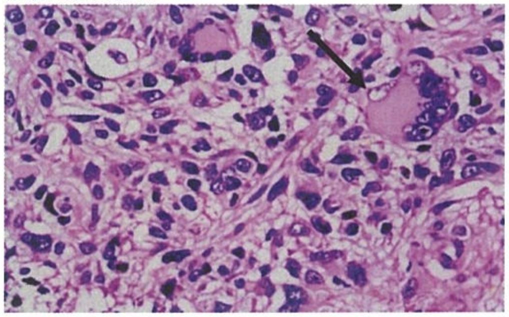
OTHER HIGH YIELD POINTS

- IHC:
  - Glial markers: (+) OLIG2; GFAP may be positive, negative, or absent
  - EMA and cytokeratin cocktails are sometimes positive, probably due to cross-reactivity with GFAP
  - (-) CAM 5.2
- Molecular: BRAF V600E is positive in younger patients

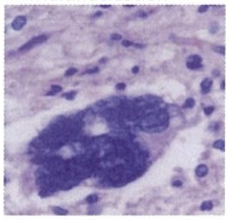
Transition between tumor cells and normal white matter



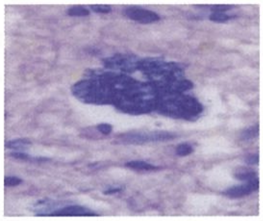
Bizarre-shaped multinucleated giant cells intermixed with small tumor cells



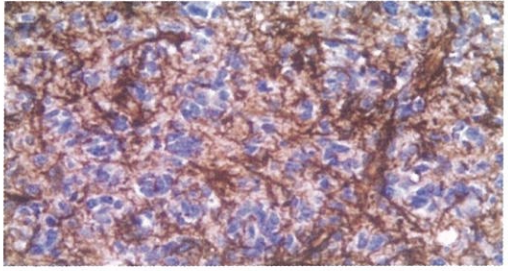
Multinucleation



Giant cell



GFAP-positive malignant cells



GIANT CELL GLIOBLASTOMA (CNS WHO GRADE 4)

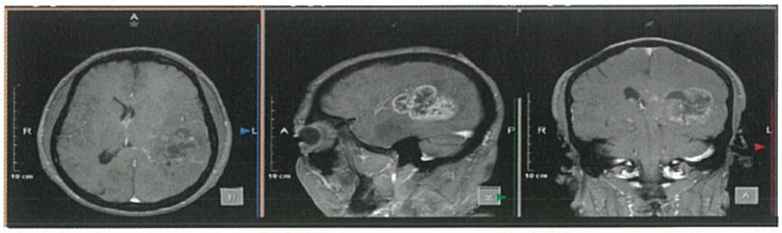
B

MORPHOLOGY

- Histologic subtype of glioblastoma, IDH-wildtype
- Composed of a dominant number of **"bizarre" giant cells** as large as 0.5 mm in diameter, which may contain **a few to > 20 nuclei**
- Other features: Mitosis in giant cells and smaller tumor cells, perivascular accumulation of tumor cells with a pseudorosette-like pattern, palisading or large ischemic necrotic zones, perivascular lymphocyte cuffing, sharp margins, and reticulin-rich areas in a background of small, often fusiform tumor cells
- Gross exam: Well-circumscribed, firm lesions

OTHER HIGH YIELD POINTS

- Clinically presents de novo after a short preoperative history
- 1% of all glioblastomas
- More commonly occurs subcortically in the temporal and parietal lobes
- Most common in the 1st-2nd decades of life with an M:F ratio of 1.1-1.5:1
- **Poor prognosis**
- IHC:
  - Glial markers: (+) GFAP, OLIG2 (focally or diffusely) more often in small tumor cells
  - IDH1 R132H-wildtype, H3-wildtype
- Molecular: DNA repair defects by inherited or acquired mutations in POLE or DNA mismatch repair genes TP53, RB1, and NF1



Giant cell glioblastoma in a 43-year-old male with headaches, vomiting, decreased strength, impaired alertness, and speech impairment. Axial, sagittal, and coronal MRI with a parietal lesion, highlighting a neoplasm with a concentric ring and edema

Picture courtesy: José A. Granados, MD and Edwin R. Sanchez, MD

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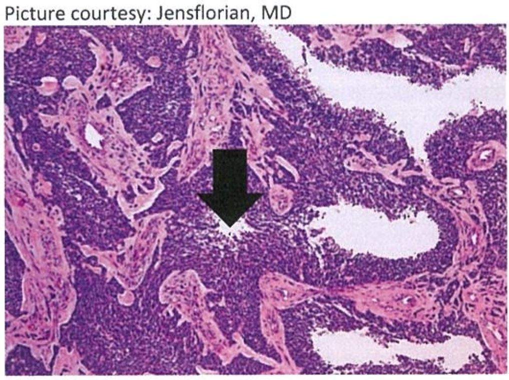
Primitive neuronal-appearing (embryonal) component (arrow)
Picture courtesy: Jensflorian, MD



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GLIOBLASTOMA WITH PRIMITIVE NEURONAL COMPONENT (CNS WHO GRADE 4)

C

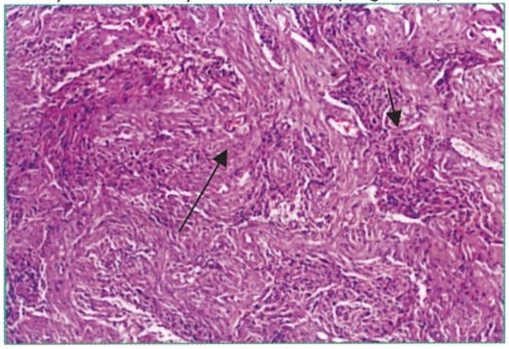
MORPHOLOGY

- Histologic subtype of glioblastoma, IDH-wildtype
- Composed of primitive neuronal (embryonal) cells with increased cellularity, high N:C ratio, brisk mitotic activity with apoptotic bodies, nuclear molding, and sometimes neuroblastic rosettes
- Other features: Infiltrating astrocytic component

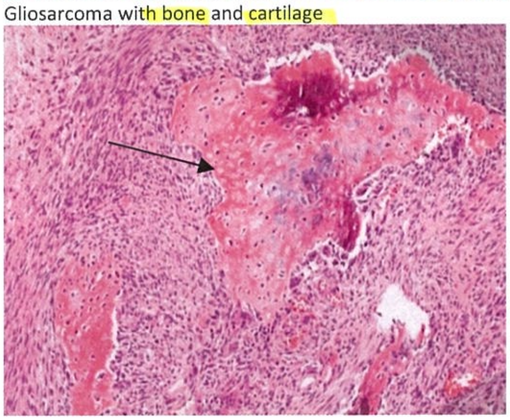
OTHER HIGH YIELD POINTS

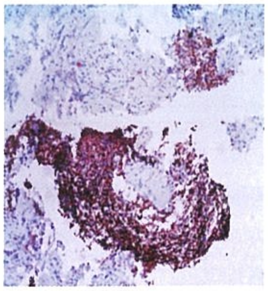
- Clinically arises de novo or as a progression from a known diffuse glioma
- Higher risk of CSF dissemination
- Prognosis and survival rate same as classic glioblastoma
- IHC: (-) OLIG2; (+) synaptophysin; GFAP negative or focally positive; Ki-67 markedly elevated (higher than other subtypes)
- Molecular: **MYC amplification**

Biphasic architecture displaying glial component (short arrow) and mesenchymal component (long arrow)

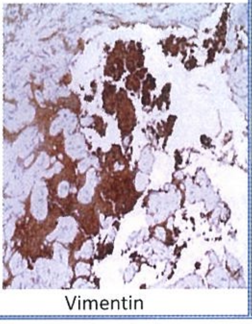


Gliosarcoma with bone and cartilage





GFAP



Vimentin

GLIOSARCOMA (CNS WHO GRADE 4)

D

MORPHOLOGY

- Histologic subtype of glioblastoma, IDH-wildtype
- Composed of a biphasic pattern with alternating areas displaying glial and mesenchymal differentiation with high-grade features (mitoses, microvascular proliferation, and/or necrosis)
- Glial component: Islands or nests of fibrillary or gemistocytic astrocytoma cells which have no reticulin
- Sarcomatous component: Long, densely packed bundles of spindle cells surrounded by reticulin fibers
- Other features: Less common formation of cartilage, bone, osteoid-chondroid tissue, smooth and striated muscle, lipomatous features, or with primitive neuronal component
- Gross exam: Well-circumscribed, firm lesions

OTHER HIGH YIELD POINTS

- Clinically presents de novo or secondarily after adjuvant treatment for high-grade glioma
- 2% of all glioblastomas
- More commonly occur in temporal lobes followed by frontal, parietal, and occipital lobes and less commonly posterior fossa, lateral ventricles, and spinal cord
- Most common in patients 40-60 years old (mean age: 52), rare in children with an M:F ratio of 1.4-1.8:1
- **Poor prognosis**
- IHC:
  - ➢ Glial markers: (+) GFAP; (-) IDH1 R132H (wildtype)
  - ➢ Sarcomatous markers: (+) vimentin; reticulin can also help defining sarcomatous areas
- Molecular: PTEN mutations, CDKN2A deletions, TP53 mutations, EGFRA amplification, +7/-10, loss of chromosomes 9 and 10

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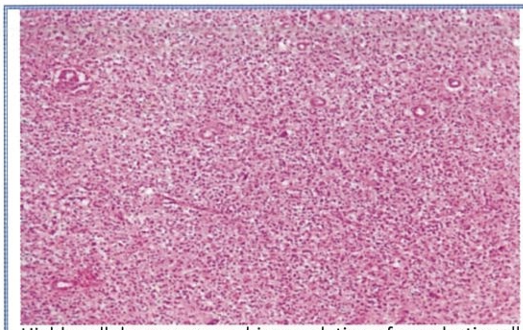
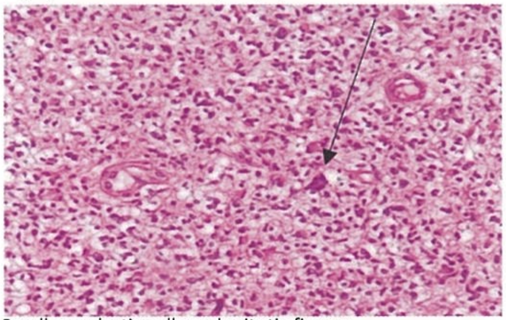


Highly cellular monomorphic population of neoplastic cells



Small neoplastic cells and mitotic figures

SMALL CELL GLIOBLASTOMA (CNS WHO GRADE 4)

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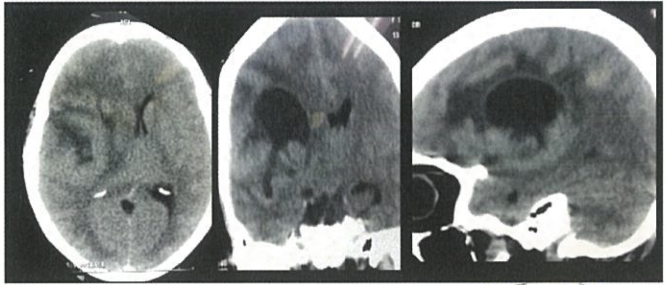
MORPHOLOGY

- Histologic subtype of glioblastoma, IDH-wildtype
- Composed of small, round to slightly elongated, monomorphic cells with hyperchromatic nuclei, minimal cytoplasm, and scarce nuclear atypia which mostly show brisk mitotic activity
- Other features: Clear halos, microcalcifications, and chicken wire-like microvasculature

OTHER HIGH YIELD POINTS

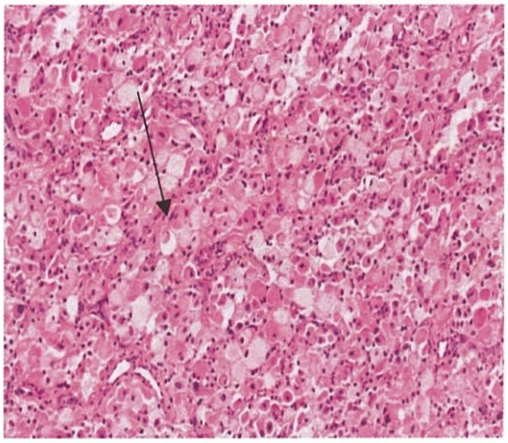
E

- **Poor prognosis**
- IHC: (+) GFAP; Ki-67 high
- Molecular: EGFR amplification in 70% and chromosome 10 loss in > 95%



Glioblastoma. Axial, coronal, and sagittal CT showing a hyperintense lesion surrounded by a hypointense area of edema

?



Glioblastoma with numerous granular cells

GRANULAR CELL GLIOBLASTOMA (CNS WHO GRADE 4)

F

MORPHOLOGY

- Histologic subtype of glioblastoma, IDH-wildtype
- Composed of an extensive number of large cells with a granular, PAS-positive cytoplasm that contains lysosomes
- Other features: Granular cells may resemble macrophages

OTHER HIGH YIELD POINTS

- Prognosis same as conventional glioblastoma
- IHC: GFAP may be negative or peripherally positive; (+) CD68; (-) CD163

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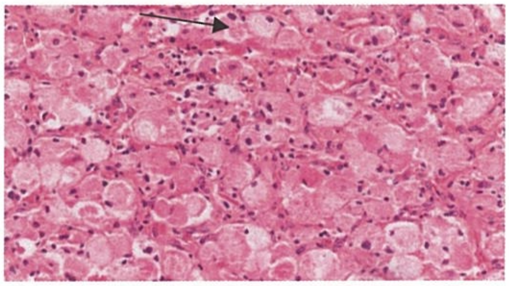
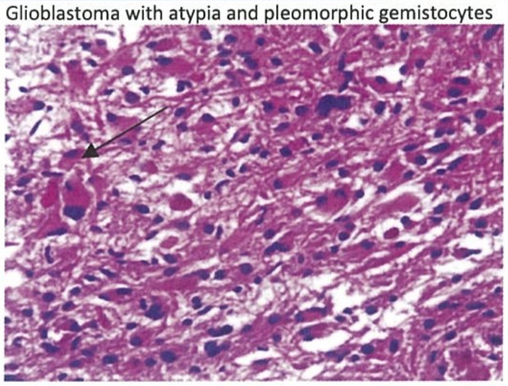
Eosinophilic changes with discrete nuclear atypia



Glioblastoma with atypia and pleomorphic gemistocytes



GLIOBLASTOMA WITH GEMISTOCYTES (CNS WHO GRADE 4)

G

MORPHOLOGY

- Histologic pattern of glioblastoma, IDH-wildtype
- Composed of gemistocytes (stubby-glassy cells containing non-fibrillary cytoplasm that have processes radiating from the cytoplasm which displace the nucleus to the periphery) and infiltrating astrocytic component

OTHER HIGH YIELD POINTS

- Gemistocytes may be present in other IDH-mutant tumors
- May resemble astrocytoma
- Prognosis and survival rate same as classic glioblastoma
- IHC: (-) GFAP, OLIG2

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GLIOBLASTOMA WITH EPITHELIAL METAPLASIA (CNS WHO GRADE 4)

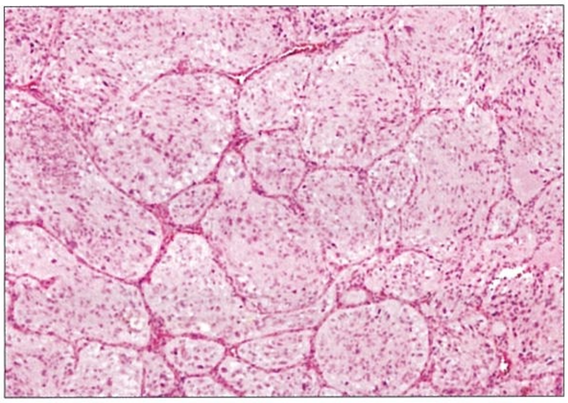
H

MORPHOLOGY

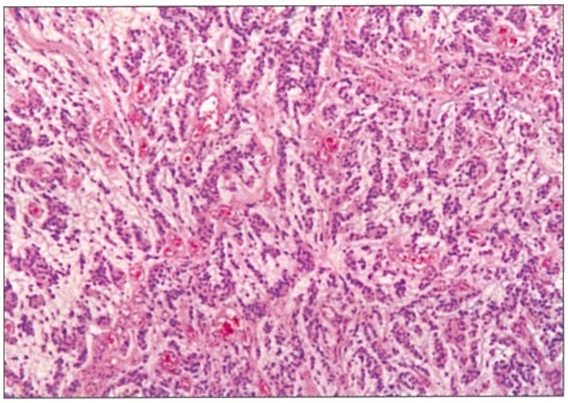
- Histologic pattern of glioblastoma, IDH-wildtype
- Composed of areas of squamous or adenomatous differentiation showing features of squamous epithelial cells including whorls with keratin pearls or foci of glandular and ribbon-like epithelioid structures that mimic metastatic adenocarcinoma

OTHER HIGH YIELD POINTS

- May be referred to as "adenoid glioblastoma" if glial immunophenotype is retained or "glioblastoma with epithelial metaplasia" when immunophenotype is truly epithelial
- These features are more common in gliosarcoma than ordinary glioblastoma
- Prognosis and survival rate same as classic glioblastoma
- IHC: (+) GFAP

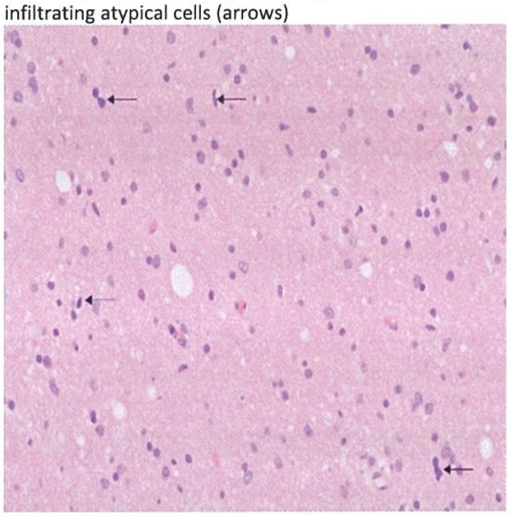


Glioblastoma with nested epithelial appearance
Pictures courtsey: Jensflorian, MD



Glioblastoma with adenoid formations on a mucinous background

An example of molecularly defined glioblastoma with few infiltrating atypical cells (arrows)



46-year-old female with headaches was found to have the MRI as shown on right; underwent biopsy, specimen was sent to next-generation sequencing that revealed TERT promoter - 124 C > T along with PTEN mutation

Picture courtesy: Raquel Yokoda, MD

GLIOBLASTOMA, MOLECULARLY DEFINED (CNS WHO GRADE 4)

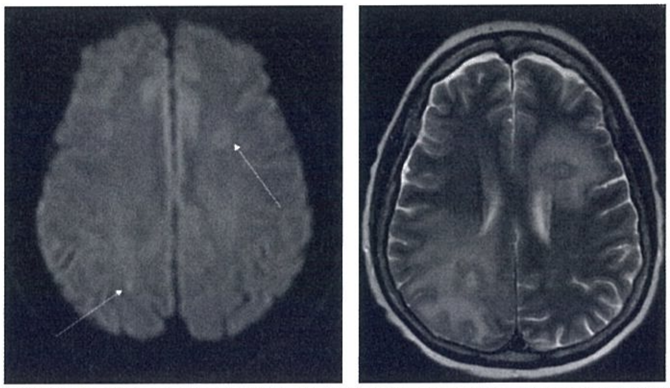
J

MORPHOLOGY

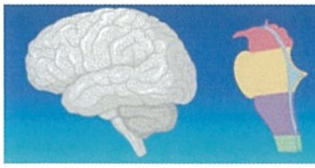
- Histologic pattern can be only a few infiltrating atypical cells with no necrosis, no microvascular proliferation, and no mitoses seen

OTHER HIGH YIELD POINTS

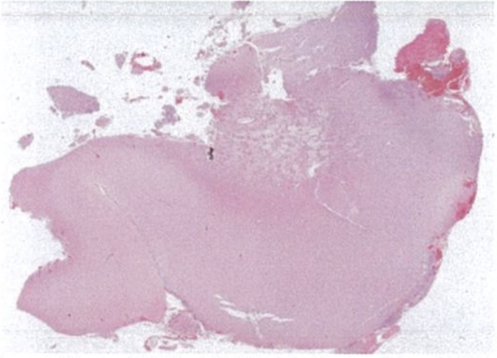
- May be referred to as "molecular glioblastoma"
- Astrocytic infiltrating pattern, IDH-wildtype, H3-wildtype with at least 1 of the following molecular findings
  - ➢ TERT promoter - 124 C > T
  - ➢ +7/-10 chromosome copy number alterations
  - ➢ EGFR amplification
- Radiology may show only subcentimeter hyperintensity



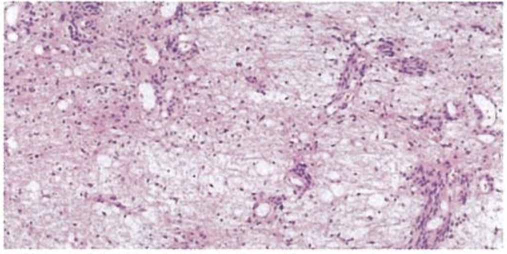
Initial MRI revealing a molecularly defined glioblastoma and a follow-up MRI 6 months after starting treatment



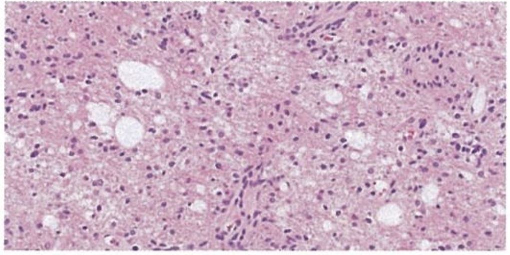
Astrocytoma (grade 2)



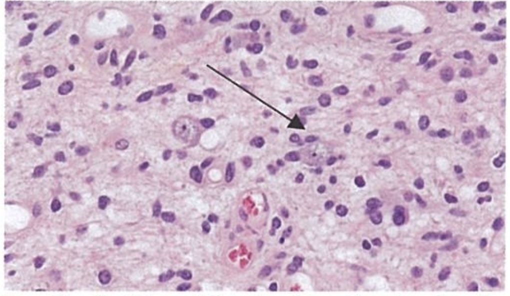
Areas of low cellularity with tiny blood vessels (grade 2)



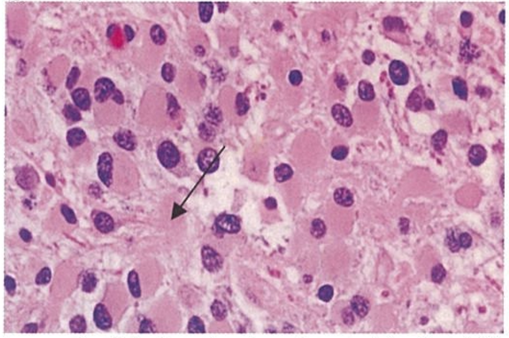
Diffuse infiltrative lesion (grade 2)



Elongated “naked nuclei” and perineuronal satellitosis



Gemistocytic differentiation (gemistocytic astrocytoma) (grade 2)



Increased cellularity and nuclear pleomorphism (grade 3)

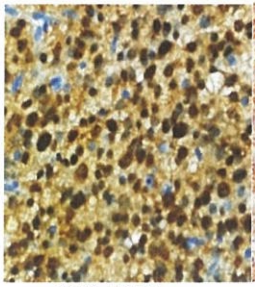
ASTROCYTOMA, IDH-MUTANT (CNS WHO GRADE 2-4)

MORPHOLOGY

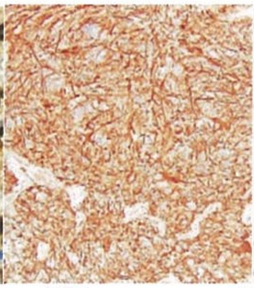
- **Diffusely** infiltrating astrocytic neoplasm composed of fibrillary glial cells that infiltrate the CNS with a **mutation in either IDH1 or IDH2 and intact chromosomes 1p and 19q**
- Features that **favor neoplastic-type atypia over reactive atypia**:
  - ➢ Increased nuclear size and nuclear contour irregularity
  - ➢ Hyperchromasia and irregular chromatin distribution
  - ➢ Clustering of atypical cells, hypercellular
  - ➢ Secondary structures of Scherer (indicative of **infiltrative growth**)
- **Grade 2**: Well-differentiated fibrillary astrocytes with all of the following:
  - ➢ Mild to moderate cellularity and nuclear atypia
  - ➢ Loose fibrillary or microcystic/cobweb-like background (previously known as fibrillary and protoplasmic variants)
  - ➢ Lack of significant mitotic activity
  - ➢ Negative for CDKN2A/B homozygous deletion
- **Grade 3** has all of the following:
  - ➢ Moderate to marked cellularity with increasing nuclear atypia
  - ➢ **Brisk mitotic activity**
  - ➢ **Negative for CDKN2A/B** homozygous deletion
- **Grade 4**: Increased cellularity and mitotic activity with at least 1 of the following (substantial **histologic overlap with glioblastoma**, IDH-wildtype):
  - ➢ Microvascular proliferation
  - ➢ Pseudopalisading necrosis
  - ➢ **CDKN2A/B homozygous deletion**

OTHER HIGH YIELD POINTS

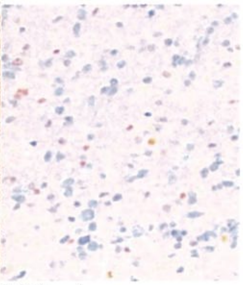
- The terms “diffuse”, “anaplastic”, and “glioblastoma” are no longer applied to IDH-mutant gliomas; gemistocytic astrocytoma (> 20% gemistocytes) is currently under the umbrella of IDH-mutant astrocytomas and is now known as “astrocytoma, IDH-mutant, grades 2 or 3”
- Young adults commonly present with new-onset seizure
- Most commonly found **supratentorially**, usually frontal lobes; may affect any region of the CNS including the brainstem and spinal cord
- IHC**: IDH1 R132H mutation** most common (immunostain available)
- IDH1/2 gene sequencing may be necessary to identify non-canonical IDH mutations (especially if the patient’s age < 55 years old)
- Molecular: **Mutations in ATRX** (loss of nuclear immunostaining) and TP53 (strong nuclear p53 expression) are common
- CDKN2A/B homozygous deletion is strongly associated with poor prognosis And is diagnostic of grade 4, even without high-grade histology



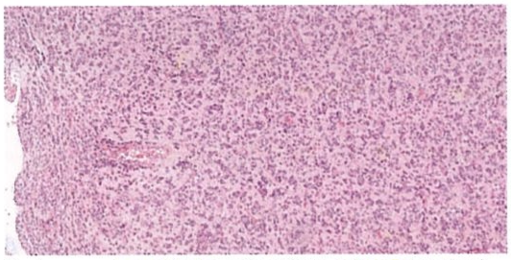
IDH1 R132H



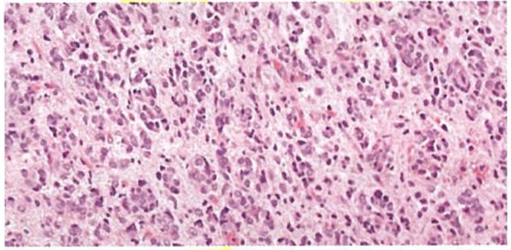
GFAP



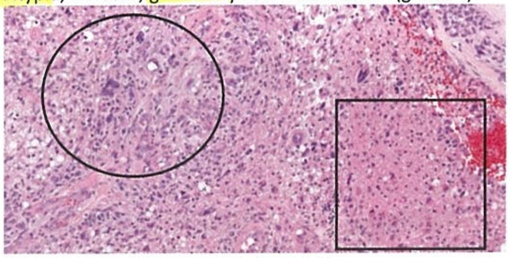
ATRX (loss)



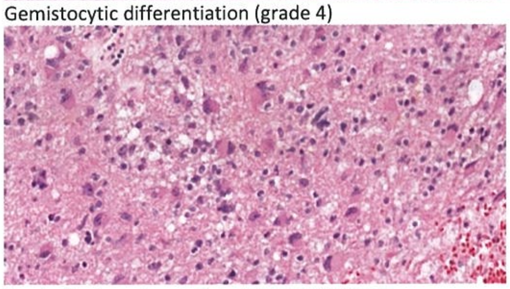
Perineuronal satellitosis and multiple mitoses (grade 3)



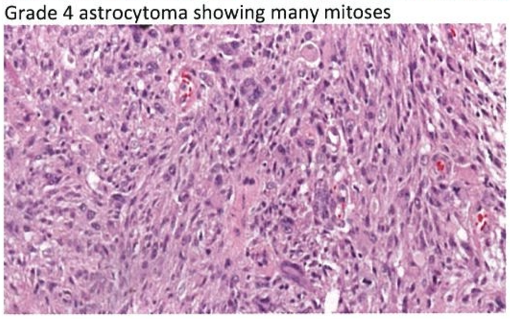
Atypia, mitoses, gemistocytic differentiation (grade 4)

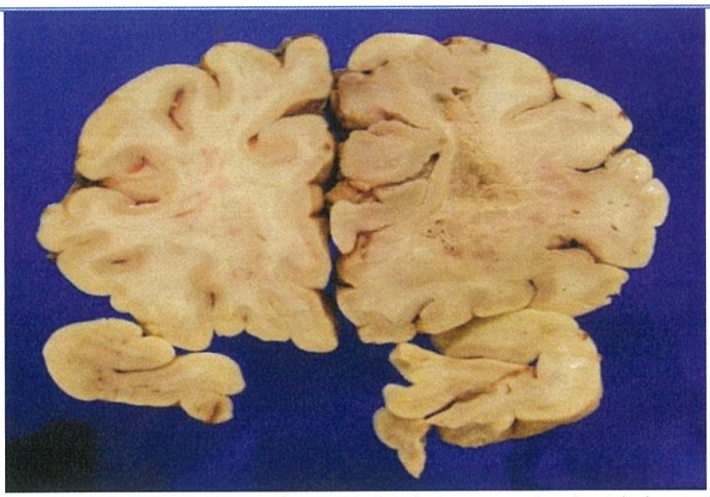


Gemistocytic differentiation (grade 4)

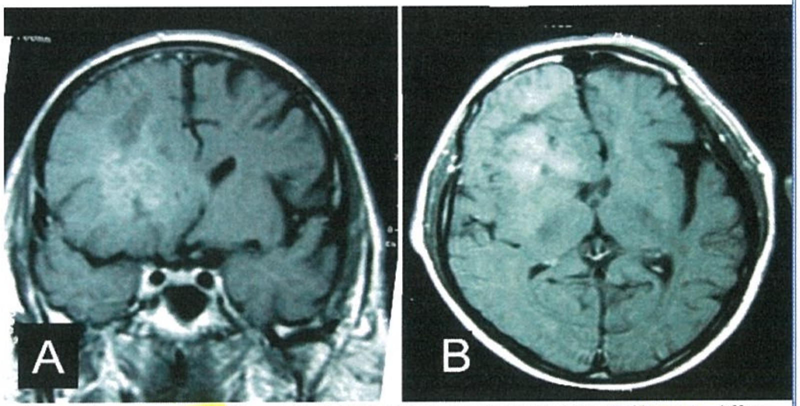


Grade 4 astrocytoma showing many mitoses

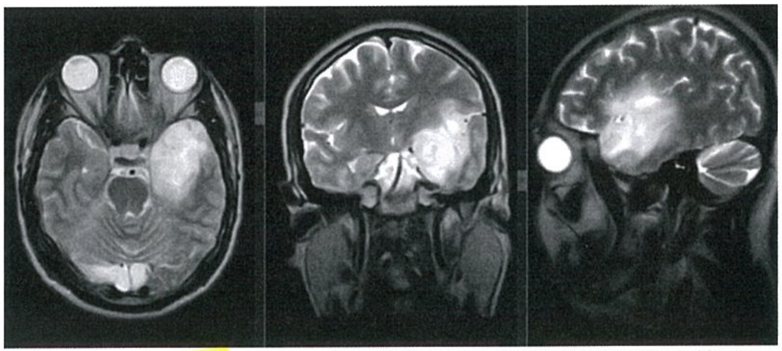




Astrocytoma, grade 2. Diffuse, granular, gray-white lesion occupying the right hemisphere and extending into the frontal-parietal lobes
Picture courtesy: Eduardo González, MD and María de la Paz Espinoza, MD



Astrocytoma, grade 2. T1-weighted MRI of the case above showing infiltrative, diffuse lesion in the frontal right lobe



Astrocytoma, grade 3. Axial, coronal and sagittal MRI show a diffuse temporal lesion
Picture courtesy: Paulo Rubio, MD and Dr. Sofia M. Flores

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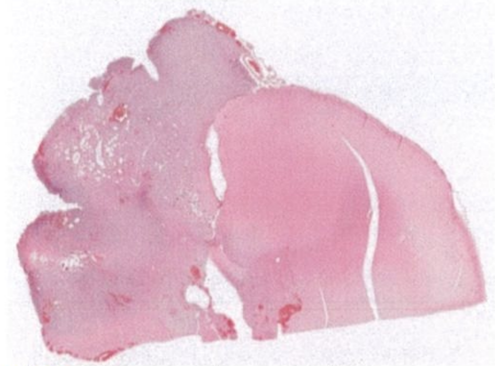
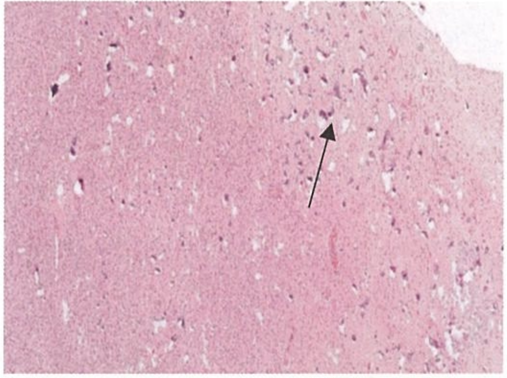
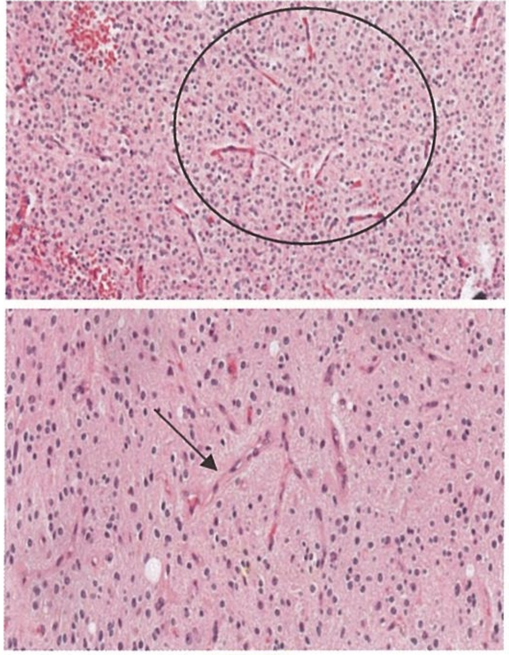
Whole-mount section shows a cortical-centric lesion that thickens the cortical ribbon



Diffuse infiltrative growth pattern and large, laminated calcospherites



Delicate vascular branching network ("chicken wire" or "honeycomb" vasculature) in both low- and high-power magnification



Laminated concentric calcifications

OLIGODENDROGLIOMA, IDH-MUTANT AND 1p/19q-CODELETED (CNS WHO GRADE 2-3)

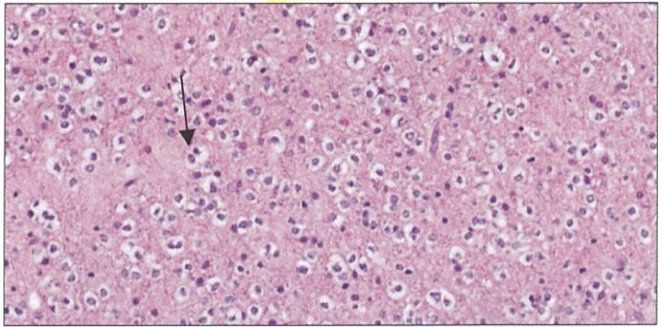
MORPHOLOGY

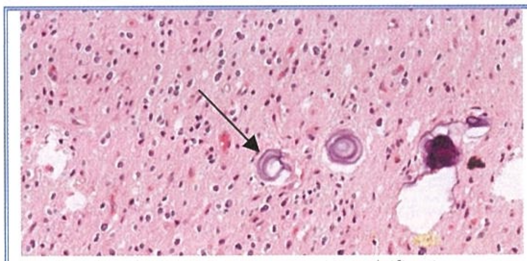
- Diffusely infiltrating glial neoplasm with a **mutation in either IDH1 or IDH2 and codeletion of chromosomes 1p and 19q**
- Monomorphic, monotonous cells with round nuclei that have perinuclear halos (**"fried eggs"**, a formalin fixation artifact which will not be seen on a frozen section or smear preparation) or honeycomb appearance
- Dilated, branching capillaries (**"chicken wire" appearance**)
- Other features: Microcalcifications (calcospherites), mucoid/cystic degeneration forming microcysts, round nuclei with small prominent nucleoli, palisades or cohesive clusters of cells, circumscribed nodules with increased cellularity (may have atypia), cells resembling plump astrocytes (minigemistocytes and gliofibrillary oligodendrocytes)
- Gross exam: Well-delineated, grayish-pink, solid lesion with cystic degeneration, calcifications, and hemorrhage in the gray-white junction
- **Grade 2** has all of the following:
  - ➢ Moderate cellularity with **low mitotic activity**
  - ➢ **Absence of microvascular proliferation and necrosis**
- **Grade 3** has at **least 1** of the following:
  - ➢ Brisk **mitotic** activity (6 or more mitoses per 10 HPF)
  - ➢ **Microvascular proliferation**
  - ➢ **Necrosis with or without palisading**
  - ➢ May also show high cellularity and/or marked cytologic atypia

OTHER HIGH YIELD POINTS

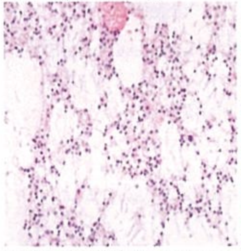
- Clinically presents with **seizures**; may present with headaches, focal neurologic deficits, signs of increased intracranial pressure, or mental changes
- More than 50% occur in the **frontal lobe**; may be present in other lobes (temporal, parietal, occipital, and in multiple lobes) as well as basal ganglia, brainstem, and spinal cord
- Most common in adults in the 3rd or 4th decades with a male predominance of 1.3:1; rare in children, although other pediatric tumors might display "oligo-like" histology and may not necessarily be oligodendrogliomas
- Imaging: T1-hypointense, well-demarcated solid lesion; T2-hyperintense lesion with cystic degeneration
- Prolonged survival compared to other adult-type diffuse gliomas
- **Recurrence and malignant progression** occur but usually at a **slower** rate compared to IDH-mutant astrocytoma and IDH-wildtype glioblastoma
- IHC: (+) IDH1 R132H mutation specific antibody, OLIG2, GFAP; ATRX nuclear expression retained and p53 expression weak (both wildtype patterns)
- Molecular: IDH1 codon 132 or IDH2 codon 172 missense mutation, combined whole arm deletions of 1p and 19q, DNA methylation profile for oligodendroglioma, and frequent **TERT** promoter mutations

Perinuclear halos with a "fried egg" appearance

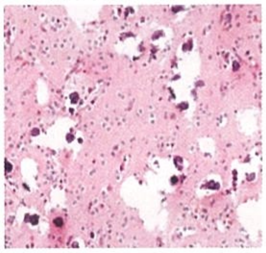




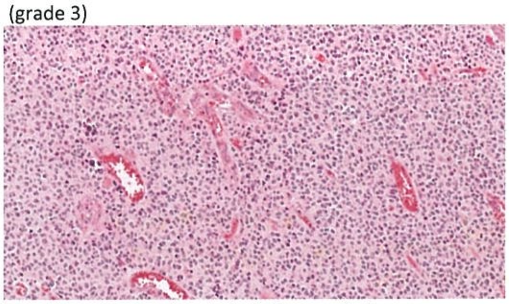
Microcystic change



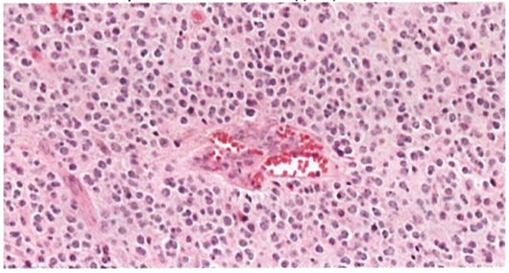
Microcalcifications

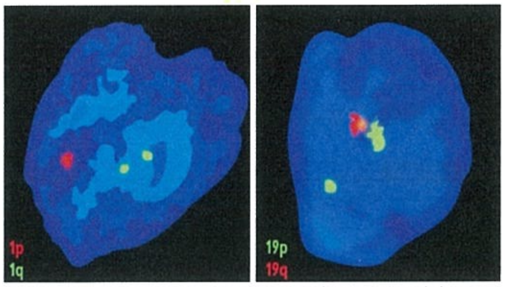


Marked cellularity, atypia, and vascular proliferation (grade 3)

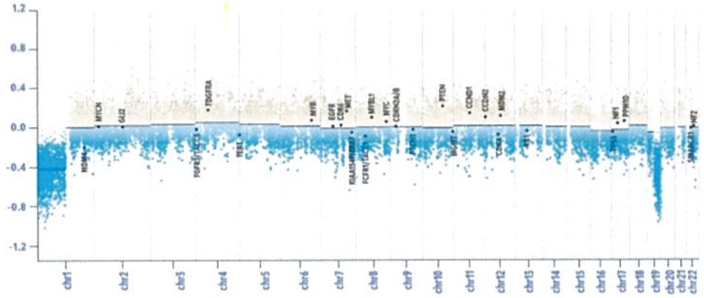


Mitotic activity and endothelial hyperplasia

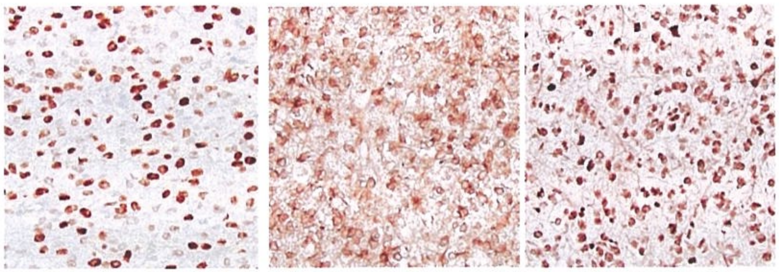




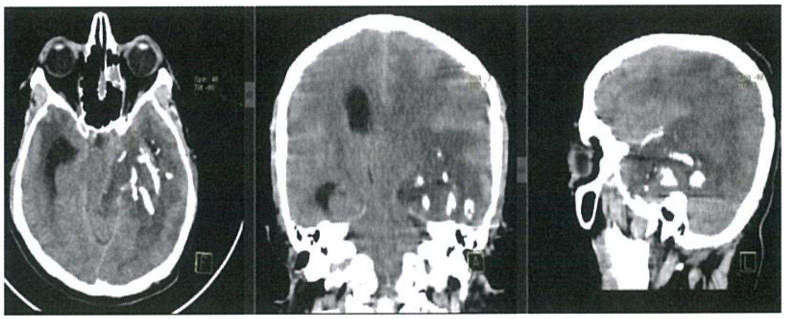
Oligodendroglioma. FISH technique showing 1p deletion (1 red and 2 greens, right) and 19q deletion (1 red and 2 greens, left)



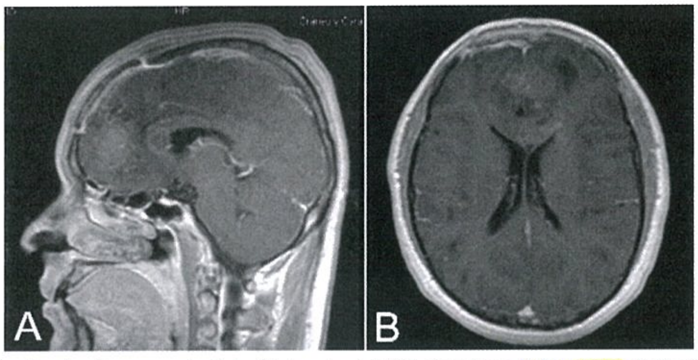
Cytogenetic profile (methylation array) prototypic for oligodendroglioma showing evidence of 1p/19q codeletion



OLIG2 IDH1 R132H ATRX (retained)



Oligodendroglioma, grade 2. Axial, coronal, and sagittal CT showing an infiltrative lesion with multiple calcifications



Oligodendroglioma, grade 2. Sagittal and axial MRI showing a diffuse lesion in the left frontal lobe with peritumoral edema

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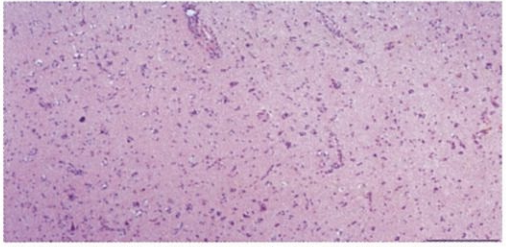
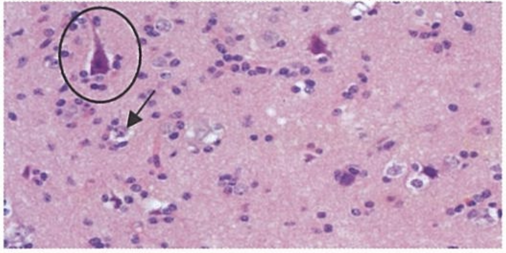
10. GLIAL TUMORS

LOW-GRADE PEDIATRIC-TYPE DIFFUSE GLIOMAS

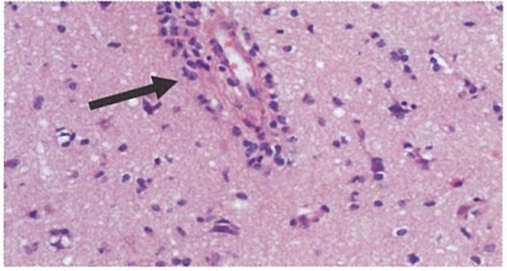
Fibrillary matrix with astrocytes



Mild hypercellularity (glial cells) and entrapped neurons



Angiocentric polarity



Picture courtesy: Wanming Hu, MD

DIFFUSE ASTROCYTOMA, MYB- OR MYBL1-ALTERED (CNS WHO GRADE 1)

MORPHOLOGY

- Diffuse infiltrative astrocytoma composed of monomorphic astrocytic cells, **MYB- or MYBL1-altered**
- Glial element features: Glial cells with nuclei that are round to ovoid or spindle-shaped, lying on a fibrillary matrix or permeating neuropil
- Other features: Regional angiocentric polarity (MYB-altered type); entrapped neurons; mitotic activity, microvascular proliferation, and mitosis usually absent; pleomorphic nuclei and slightly elevated proliferation may be seen in some pediatric cases
- Gross exam: Infiltrative, solid, gray-white, soft-friable lesion

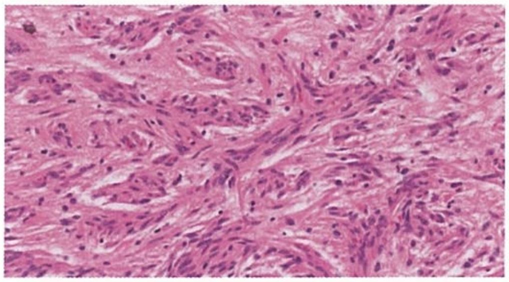
OTHER HIGH YIELD POINTS

- Clinically presents with early onset **epileptic seizures (drug resistant)**
- More than 42% occur in the **temporal lobe with a cortical-subcortical component**; may be present in other lobes (frontal, parietal, occipital as well as the brainstem
- Median age of presentation is 29 years (range: 4-50); male predominance (M:F ratio: 3:1)
- Imaging: T1-hypointense lesion; T2-hyperintense lesion; without enhancement or restricted diffusion
- **Benign prognosis** (limited clinical data)
- IHC: Glial markers: (+) GFAP; (-) OLIG2, MAP2; (-) CD34; ATRX (retained); (-) IDH1 R132H; Ki-67 low
- Molecular: **MYB- or MYBL1-altered**; fusion with partner genes (PCDHGA1, MMP16, or MAML2); IDH and H3-wildtype are both negative

ANGIOCENTRIC GLIOMA (CNS WHO GRADE 1)

MORPHOLOGY

- Diffuse infiltrative glioma composed of bland bipolar cells that aggregate in perivascular spaces (at least partially), MYB::QKI or MYB-altered
- Glial element features: Rosette-like perivascular pattern formed by single or multiple cells which are radially arranged and are spindle-shaped with slender nuclei and granular chromatin
- Other features: Spindle cells may form compact nodules of intersecting, tight fascicles arranged along the pial surface in a horizontal or perpendicular, palisading, schwannoma-like pattern
- Myxoid and microcystic alterations as well as entrapped neurons (conspicuous) are present
- Mitotic activity and microvascular proliferation are usually absent; elevated proliferation has been seen in some cases
- Gross exam: Solid, gray-tan lesion may be soft and gelatinous or produce induration and blurring of the cortical gray-white junction; cystic changes may occur



Tumor cells are elongated and have bipolar cytoplasmic processes

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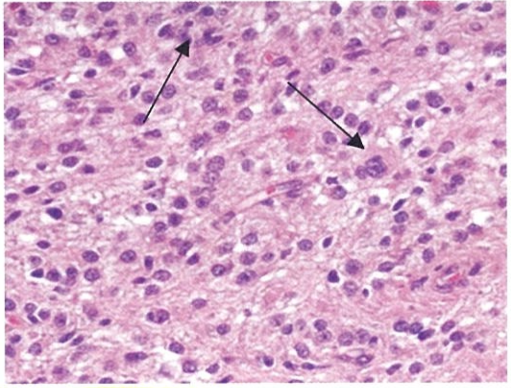
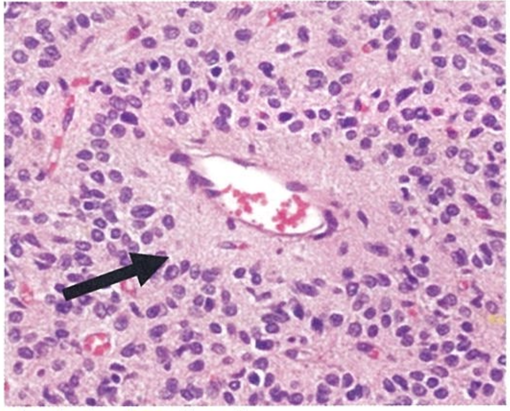
OTHER HIGH YIELD POINTS

- Clinically presents with **chronic and intractable partial epilepsy**; visual impairment and headaches may be present
- Occurs in the cerebral cortex (temporal or frontal lobes); may be brainstem
- Most common in children and young adults; slight male predominance
- Imaging: Rim-like hyperintensity surrounding the tumor on T1; T2-hyperintense, well-circumscribed lesion without contrast enhancement; dystrophic calcifications and stalk-like extension to the adjacent lateral ventricle have been described
- Recurrence uncommon, with **good prognosis**
  - ➢ IHC: Glial markers: (+) GFAP; (-) OLIG2; (+) EMA (dot- or ring-like cytoplasmic pattern), Ki-67: < 1%-5%
- **Molecular: MYB-altered (rearrangements, deletions, or amplifications at the 6q23.3 locus or MYB::QKI fusion in 87%);** IDH1, IDH2, TP53, ATRX, and histone H3 genes are negative

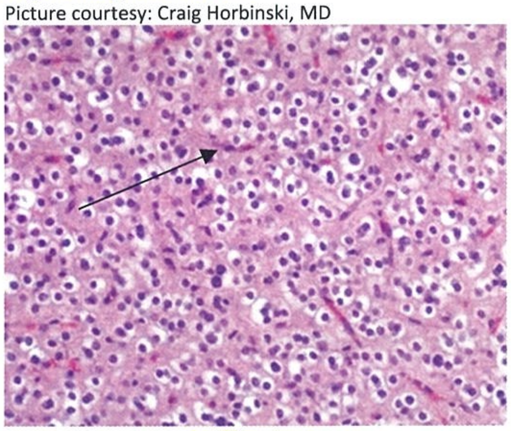
Fibrillary background with pleomorphic cellularity
Picture courtesy: Craig Horbinski, MD



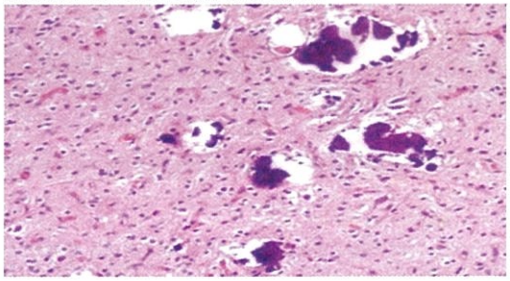
Perivascular pseudorosette
Picture courtesy: Craig Horbinski, MD



Oligodendroglioma-like cells
Picture courtesy: Craig Horbinski, MD



Areas with numerous calcifications
Picture courtesy: Craig Horbinski, MD



POLYMORPHOUS LOW-GRADE NEUROEPITHELIAL TUMOR OF THE YOUNG (PLNTY) (CNS WHO GRADE 1)

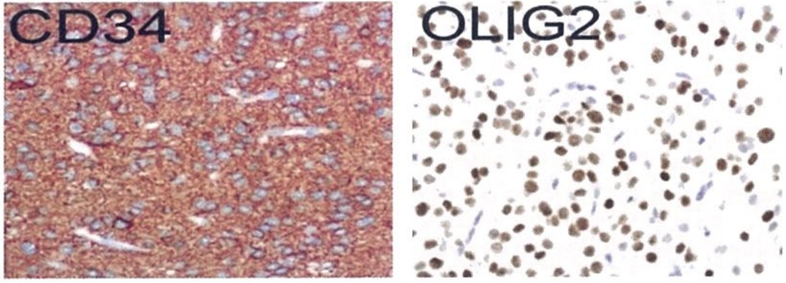
MORPHOLOGY

- Neuroepithelial tumor composed of a diffuse infiltrative pattern, oligodendroglioma-like cells, calcifications, CD34 immunoreactivity, and MAPK pathway-activating genetic abnormalities
- Glial element features: Fibrillary, spindled, or pleomorphic cells with small uniform nuclei, perinuclear halos, variation in nuclear size and shape, wrinkled and grooved nuclear membranes, and intranuclear pseudoinclusions
- Other features: Presence of eosinophilic granular bodies and occasional perivascular pseudorosettes; microvascular proliferation and mitoses are usually absent; elevated proliferation has been seen in some cases
- Gross exam: Solid or cystic lesion mostly occurring at the gray-white junction and associated with calcifications

OTHER HIGH YIELD POINTS

- Clinically presents with **seizures and refractory epilepsy, headaches, or dizziness**
- Approximately 80% occur in the **temporal lobe, mostly on the right side, with involvement of the medial/posteroinferior structures**; may be present in other lobes (frontal, parietal, occipital) as well as the 3rd ventricle
- Most common in the 2nd and 3rd decades with no sex predominance
- Imaging: T1-hypointense solid or cystic lesion; T2-hyperintense; FLAIR with increased signal
- Prognosis is favorable with relief from seizures; further follow-up needed
- IHC:
    - ➢ Glial markers: (+) GFAP, OLIG2
    - ➢ (+) CD34 (patchy, diffuse, or intense); (-) IDH1 R132H; ATRX (retained); BRAF V600E
    - ➢ Ki-67: < 1-2%
- Molecular: **MAPK pathway activation** (BRAF V600E mutation, FGFR2 or FGFR3 fusions such as FGFR2::CTNNA3, FGFR2::SHTN1 (KIA1598), FGFR2::INA, and FGFR3::TACC2)

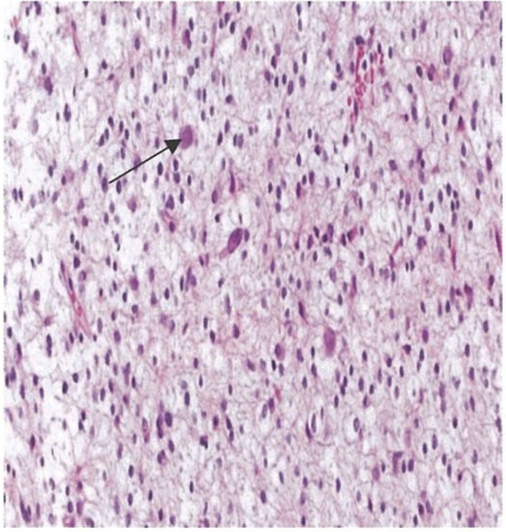
Tumor staining is diffusely and strongly positive for CD34 and shows nuclear positivity for OLIG2
Picture courtesy: Craig Horbinski, MD



On the left - Polymorphous low-grade neuroepithelial tumor of the young in a 16-year-old boy with a patchy, contrast-enhancing lesion in the temporal lobe. Next-generation sequencing showed BRAF V600E
Picture courtesy: Craig Horbinski, MD

10. GLIAL TUMORS

Small neoplastic cells with entrapped neurons



DIFFUSE LOW-GRADE GLIOMA, MAPK PATHWAY-ALTERED (NOT CURRENTLY GRADED)

MORPHOLOGY

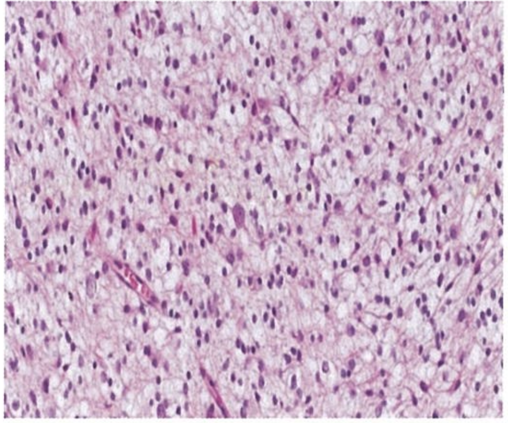
- Diffuse low-grade glioma composed of astrocytic or oligodendroglial-like cells, MAPK pathway-altered
- **3 subtypes:**
    - ➢ Diffuse low-grade glioma, FGFR1 tyrosine kinase domain-duplicated
    - ➢ Diffuse low-grade glioma, FGFR1-mutant
    - ➢ Diffuse low-grade glioma, BRAF p.V600E-mutant

OTHER HIGH YIELD POINTS

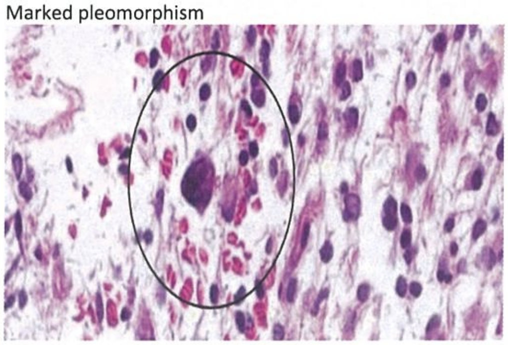
- Clinically presents with epilepsy; may vary according to size and localization of tumor
- Common in cerebral hemispheres; may arise along the craniospinal axis
- More common in children
- Imaging: Diffuse lesions or heterogeneously enhancing mass with cysts
- Prognosis uncertain
- IHC:
    - ➢ Glial markers: (+) GFAP (variable), OLIG2
    - ➢ (+) CD34 (focal)
    - ➢ BRAF V600E (positive when mutation is present)
- Molecular: MAPK pathway alterations, IDH and H3-wildtype; **absence of homozygous deletion of CDKN2A**

HIGH-GRADE PEDIATRIC-TYPE DIFFUSE GLIOMAS

Diffuse infiltration of monomorphic cells



Marked pleomorphism



DIFFUSE MIDLINE GLIOMA, H3 K27-ALTERED (CNS WHO GRADE 4)

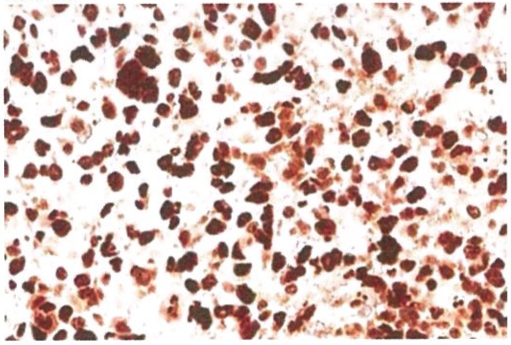
MORPHOLOGY

- Diffusely infiltrating midline glioma with astrocytic differentiation which has H3 K27M alteration
- Tumor cells are usually small and monomorphic
- Mitosis, microvascular proliferation, and/or necrosis may be seen but are **not necessary for the diagnosis** or grade 4 designation
- **Other features**: Astrocytic, piloid, oligodendroglial, giant cell, undifferentiated, or epithelioid cell cytology may be encountered; usually lacks perivascular or perineuronal satellitosis
- Gross exam: Solid lesion with diffuse infiltration causing distortion of adjacent midline structures with areas of necrosis and hemorrhage

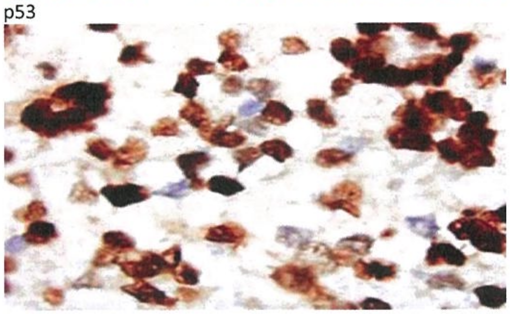
OTHER HIGH YIELD POINTS

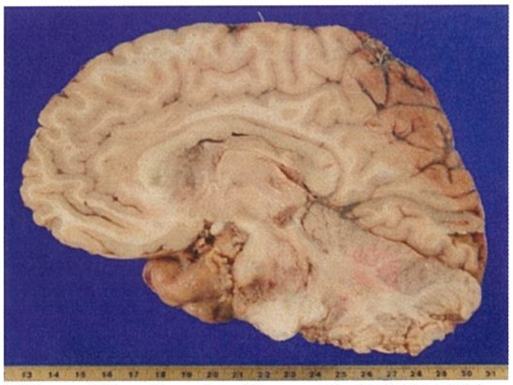
- Clinically presents with **a classic triad: cranial nerve palsy, ataxia, and long tract signs such as pyramidal tract impairment (< 2 months)**; thalamic presentation with motor or sensory deficit and intracranial hypertension; may vary according to size and localization of tumor
- More commonly occurs in children in the **brainstem or pons, which is also known as diffuse intrinsic pontine glioma (DIPG) or as a bithalamic lesion**; in adolescents and adults, usually found as a unilateral lesion in the thalamus or spinal cord; may be present in hypothalamus, cerebellum, and pineal gland
- Leptomeningeal involvement may be found in 40%; diffuse infiltration to the thalamus, frontal lobe, and cervical cord in some cases
- Associated with Li-Fraumeni syndrome or mismatch repair deficiency
- Imaging: DIPGs classically have an epicenter in the pons and involve more than 50% of its surface, often asymmetrically with frequent encasement of the basilar artery. There may be an exophytic component and/or infiltration into the midbrain, the cerebellar peduncles, and the cerebellar hemispheres; thalamic tumor may be unilateral or bilateral (more frequent in the EGFR-mutant subtype

H3K27M



p53





Diffuse midline glioma in a 13-year-old girl. Midsagittal cut surface showing a brainstem (pons) lesion with hemorrhage and necrosis causing compression of the 4th ventricle
Picture courtesy: Silvia J. Hernández, MD

- Lesion appears hypo- or isointense on T1-weighted MRI; T2 hyperintensity, FLAIR, and contrast enhancement patterns may vary; many tumors lack contrast enhancement
- **Poor prognosis (< 2 years)**
- IHC: (+) **H3 K27M mutation specific antibody**, GFAP, OLIG2; loss of H3K27me3 nuclear expression
- Molecular: H3 K27M (most common), H3 K27I, EGFR mutation/amplification, EZHIP overexpression, or methylation profile of diffuse midline glioma; **TP53 and/or ATRX mutations** are occasionally seen

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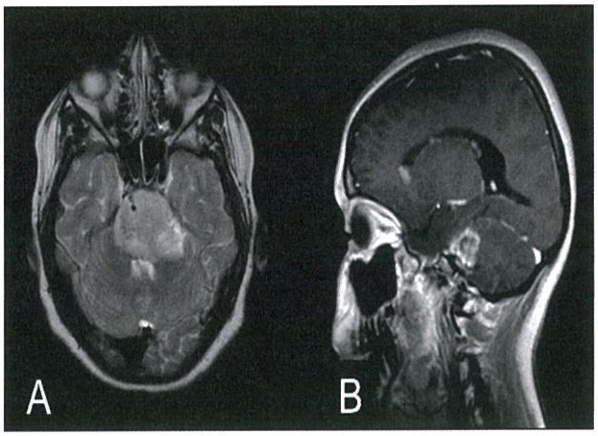
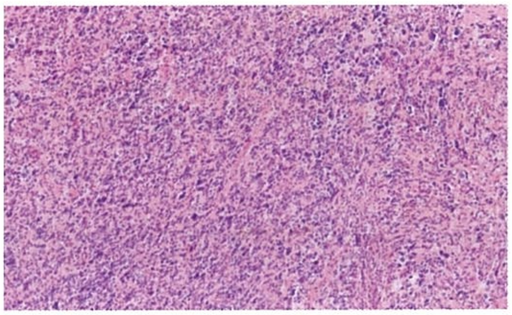


Diffuse midline glioma (same case as gross image). Axial and sagittal T2-weighted MRI showing a heterogeneous, infiltrative, diffuse lesion with ring enhancement and necrosis
Picture courtesy: Juan José Padilla, MD



High cellularity, atypia, marked pleomorphism

DIFFUSE HEMISPHERIC GLIOMA, H3 G34-MUTANT (CNS WHO GRADE 4)

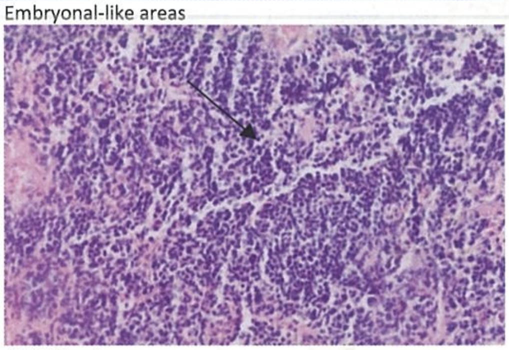
MORPHOLOGY

- Diffuse infiltrative highly cellular hemispheric glioma composed of a glioblastoma-like pattern with HE G34 mutation
- Glial element features: Brisk mitotic activity, microvascular proliferation and/or necrosis, multinucleated and pleomorphic cells
- Other features: Small, embryonal-like, monomorphic cells with hyperchromatic nuclei, scant cytoplasm, and occasional Homer Wright rosettes; ganglion cell differentiation may be present
- Gross exam: Diffuse infiltrative lesion with hemorrhage and necrosis

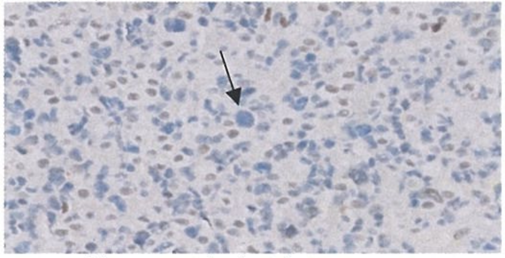
OTHER HIGH YIELD POINTS

- Clinically, may vary according to the size and location of the tumor
- Occurs in the **cerebral hemispheres or multifocally**; may spread to midline structures and leptomeninges
- Most common in adolescents and young adults with male predominance

Embryonal-like areas

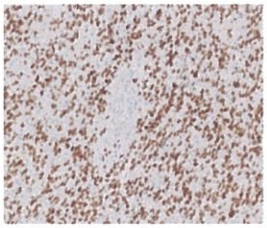


ATRX (loss)

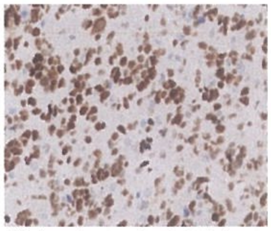


22-year-old woman with a brain lesion
Pictures courtesy: Felipe D´Almeida Costa, MD

- Imaging: Contrast-enhancing tumor with mass effect in the cortex; may have necrosis, hemorrhage, cystic changes, or calcifications
- **Poor prognosis**
- IHC:
  - (+) MAP2, FOXG1; (-) ATRX (loss of expression)
  - **Glial markers: (+/-) GFAP**; (-) OLIG2
  - (+) p53 (diffuse); Ki-67: high**; positive for H3.3 p-G35R (G34R)** and **p.G35V (G34V)**
- Molecular: **H3.3 p-G35R (G34R) or G35V (mutation) H3-3A (H3F3A) c.103G > A, c.103G > C, or c.104 G > T**

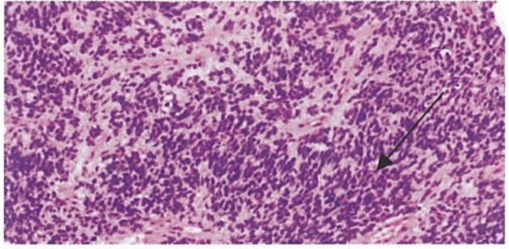


H3 G34R IHC positivity showing mutation

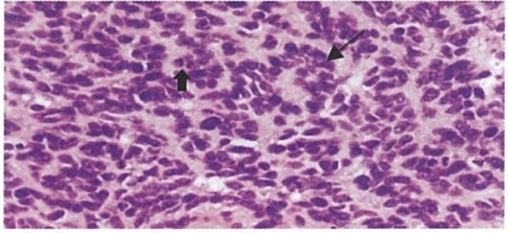


p53 showing mutant staining pattern

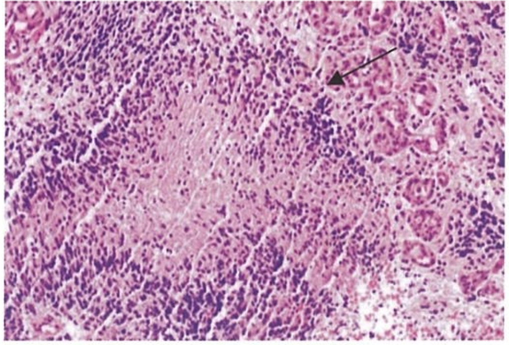
Neoplastic cells with pleomorphism



Embryonal-like primitive cells



Palisading necrosis



Teenager with enhancing temporal lobe mass. Next-generation sequencing with wildtype IDH1/2 and H3 genes. Methylation profile HGG, H3, and IDH-wildtype
Pictures courtesy: Jared Ahrendsen, MD

DIFFUSE PEDIATRIC-TYPE HIGH-GRADE GLIOMA, H3-WILDTYPE AND IDH-WILDTYPE (CNS WHO GRADE 4)

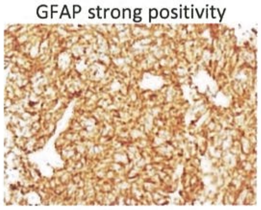
MORPHOLOGY

- Diffuse infiltrative high-grade glioma with histologic features of malignancy with H3, IDH1 and IDH2-wildtype
- **3 subtypes**:
  - Diffuse pediatric-type high-grade glioma RTK2
  - Diffuse pediatric-type high-grade glioma RTK1
  - Diffuse pediatric-type high-grade glioma MYCN
- Other features: Glioblastoma-like features (mitotic activity, vascular proliferation, and necrosis) and/or embryonal (primitive) undifferentiated cells
- Gross exam: Diffuse infiltrative lesion with hemorrhage and necrosis

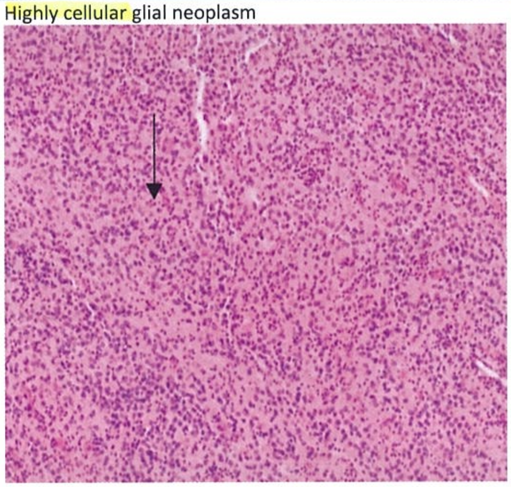
OTHER HIGH YIELD POINTS

- Clinically, may vary according to size and location of tumor; motor and sensory deficits as well as seizures
- Occurs throughout the supratentorial brain, brainstem, and cerebellum
- Imaging: Contrast-enhancing tumor with mass effect
- **Prognosis is poor** (pHGG MYN - worst, pHGG RTK1 - intermediate, pHGG RTK2 - better)
- IHC:
  - Neuronal markers present
  - Glial marker: (+) GFAP, OLIG2
  - (-) IDH1 R132H; H3 p.K28me3 (K27me3) preserved
- Molecular: H3-wildtype, IDH1- and IDH2-wildtype, **PDGFRA amplification/mutation, EGFR alteration, or MYCN amplification**

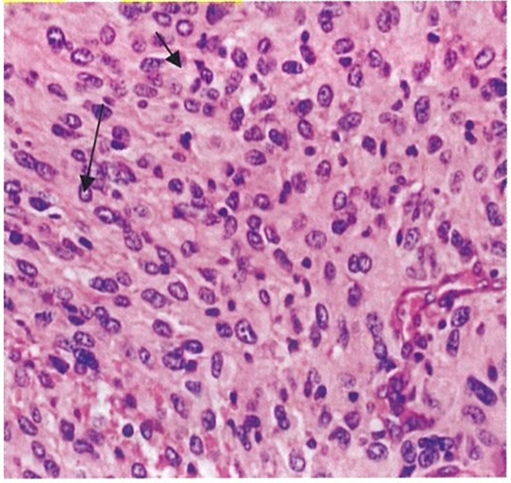
GFAP strong positivity



Highly cellular glial neoplasm



Mitosis and pleomorphism



Infant-type hemispheric glioma in a 9-month-old boy

Picture courtesy: Felipe D´Almeida Costa, MD

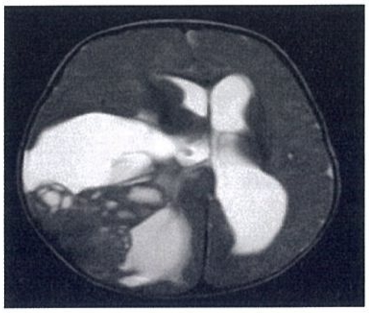
INFANT-TYPE HEMISPHERIC GLIOMA (NOT CURRENTLY GRADED)

MORPHOLOGY

- Diffuse infiltrative high-grade hemispheric glioma with receptor tyrosine kinase (RTK) fusions, including those in the NTRK family or ROS1, ALD, or MET
- 4 subtypes:
  - ➢ Infant-type hemispheric glioma**, NTRK-altered**
  - ➢ Infant-type hemispheric glioma, **ROS1-altered**
  - ➢ Infant-type hemispheric glioma, **ALK-altered**
  - ➢ Infant-type hemispheric glioma, **MET-altered**
- Glial element features: Resemble high-grade astrocytomas or ependymomas but may contain coexisting areas of low-grade and high-grade astrocytoma; astrocytic spindle-shaped cells with mild to moderate pleomorphism in fascicles or sheets as well as gemistocytes; mitotic activity, microvascular proliferation, and palisading necrosis may be present
- Other features: Embryonal (primitive) component; may involve leptomeninges; ganglion cells may be present
- Gross exam: Solid or cystic lesion with necrosis

OTHER HIGH YIELD POINTS

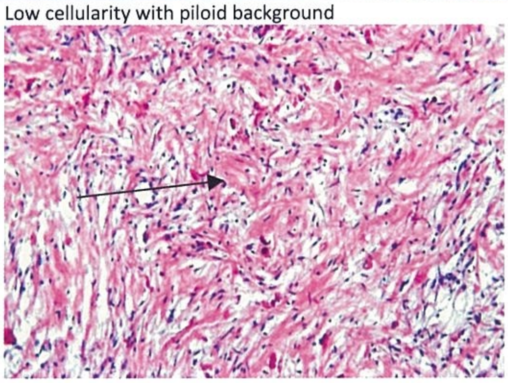
- Clinically, may present with a large head circumference
- Occurs in the supratentorial region (hemispheric)
- Most common in early childhood (< 1 year)
- More studies needed for prognosis
- IHC: **Negative for neuronal markers**
- Glial markers: (+) GFAP, (+) ALK (ALK-fusion)
- Molecular: **Tyrosine kinase abnormality** (fusion in an NTRK family gene or ROS1, MET1, or ALK)



T2-weighted MRI showing a large solid and cystic lesion in the right atrium

CIRCUMSCRIBED ASTROCYTIC GLIOMAS

Low cellularity with piloid background

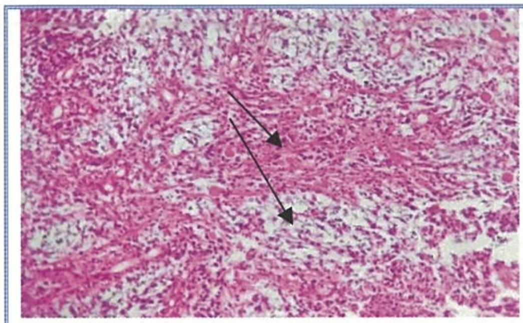


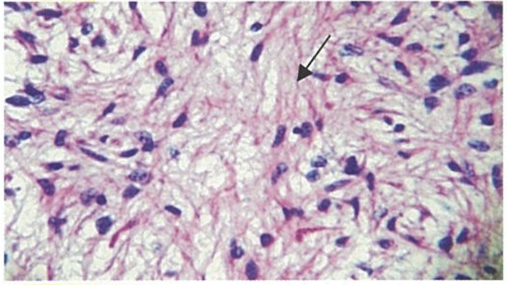
Diffuse biphasic lesion

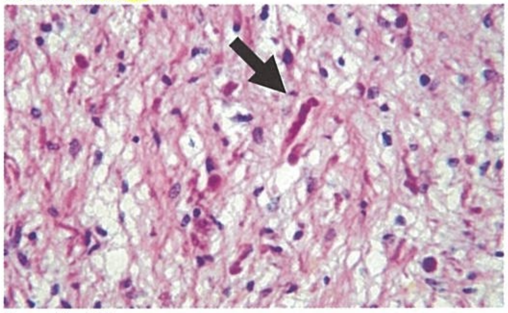
PILOCYTIC ASTROCYTOMA (CNS WHO GRADE 1)

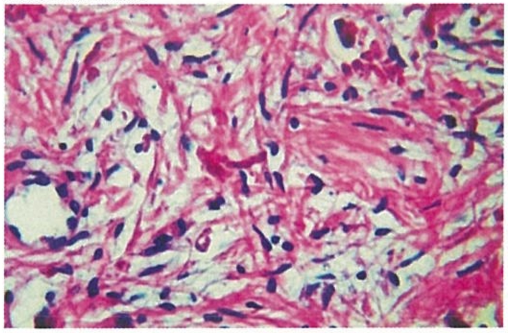
MORPHOLOGY

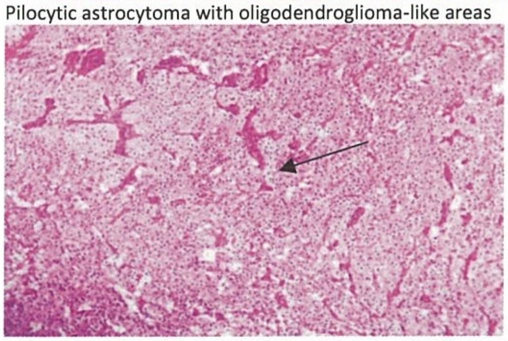
- Astrocytic neoplasm composed of variable proportions of bipolar pilocytic ("hair-like") cells and/or compact and loose or myxoid regions
- Rosenthal fibers and eosinophilic granular bodies
- Glial element features: Low to moderate cellularity, "piloid" and "**oligo-like**" components
- Other features:
  - ➢ May have multinucleated cells with horseshoe-shaped nuclear clusters (**pennies on a plate pattern**), hyperchromasia, pleomorphism but rare mitotic figures
  - ➢ Myxoid background with microcystic changes, degenerative changes such as calcifications, and intranuclear inclusions
  - ➢ Hyalinized vessels and hemorrhages, microvascular glomeruloid proliferations lining the cystic wall
  - ➢ Infarct-like necrosis and leptomeningeal invasion
- **4 histologic patterns:**
  - ➢ Biphasic pattern (alternating compact and loose regions)


"Hair-like" cells with long, slender nuclei


Rosenthal fibers


Rosenthal fibers

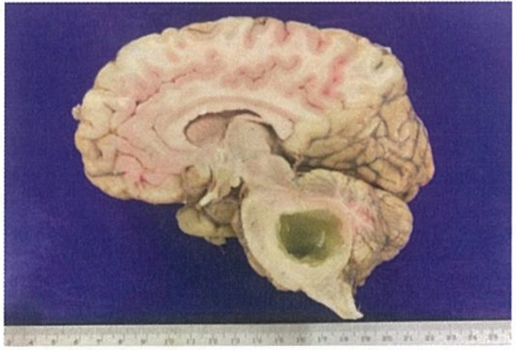

Pilocytic astrocytoma with oligodendroglioma-like areas


Intranuclear pseudoinclusions

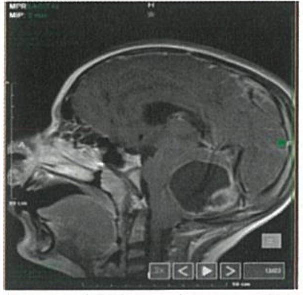
  - ➢ Compact piloid pattern (many Rosenthal fibers)
  - ➢ Dispersed pattern (many oligodendrocyte-like cells)
  - ➢ Spongioblastoma pattern (regimented palisading)
- **2 subtypes**:
  - ➢ Pilomyxoid astrocytoma (angiocentric arrangement)
  - ➢ Pilocytic astrocytoma with histologic features of anaplasia (brisk mitotic activity with or without necrosis; more common in adults)
- Gross exam: Well-delineated solid or cystic lesion with intratumoral or paratumoral cyst formation and occasional calcifications (older lesions)

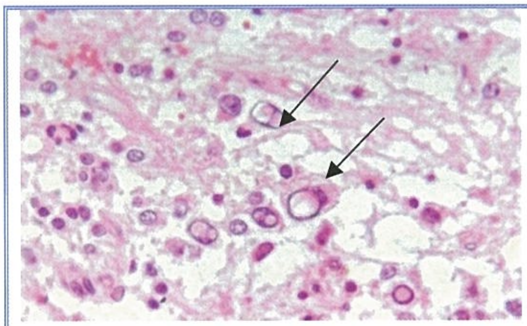
OTHER HIGH YIELD POINTS

- Clinically presents **with increased intracranial pressure, headaches, macrocephaly, or endocrinopathy**; may vary according to size and location of tumor
- More commonly occurs in the **cerebellum (children)**; may be present throughout the neuroaxis
- Can be seen in the optic nerve; midline structures like brainstem, optic chiasm/hypothalamus, basal ganglia, and spinal cord (syrinx formation); and cerebral hemispheres (adults)
- Most common in the 1st-2nd decade
- CNS tumor associated with neurodevelopmental diseases with germline mutations in MAPK pathway genes (NF1, Noonan syndrome, and encephalocraniocutaneous lipomatosis)
- Imaging: T1-hypointense, well-demarcated, solid or cystic lesion; T2-hyperintense cyst with enhancing nodule; FLAIR with increased signal; some lesions may show contrast enhancement due to microvascular proliferation
- Recurrence uncommon, with an **excellent prognosis**
- IHC: (+) **GFAP**, OLIG2, S100, SOX10, p16, neurofilament, NeuN, synaptophysin, chromogranin; (-) CD34, IDH1 R132H, H3 p.K28M (K27M); Ki-67 is low
- Molecular: **MAPK pathway alteration** (KIAA1549::BRAF fusion more common in 60%); other BRAF fusions and mutations (p.V600E); NF1, FGFR1, KRAS mutations; FGFR1, NTRK family, RAF1, ROS1 fusions; MET and RET alterations

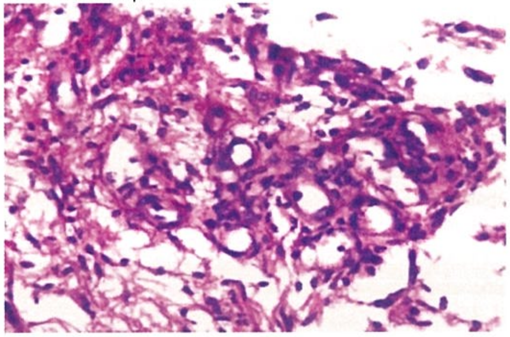

Pilocytic astrocytoma of the brainstem in a 3-year-old male. Sagittal section shows a cystic lesion in the pons with mucinous contents

Picture courtesy: Silvia J. Hernández, MD

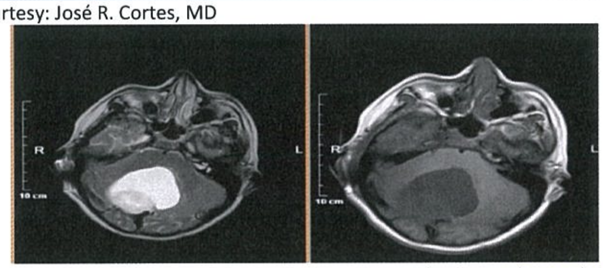

Pilocytic astrocytoma. Sagittal T1-weighted MRI showing a circumscribed cyst with a mural nodule



Microvascular proliferation

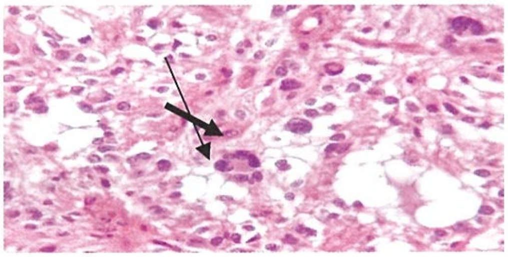


Picture courtesy: José R. Cortes, MD



Pilocytic astrocytoma. MRI showing a well-circumscribed, infratentorial cystic lesion with a mural nodule

Picture courtesy: José R. Cortes, MD



Giant cells with "pennies on a plate" appearance

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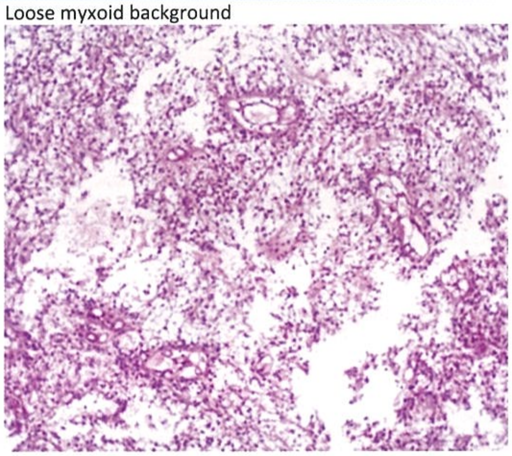
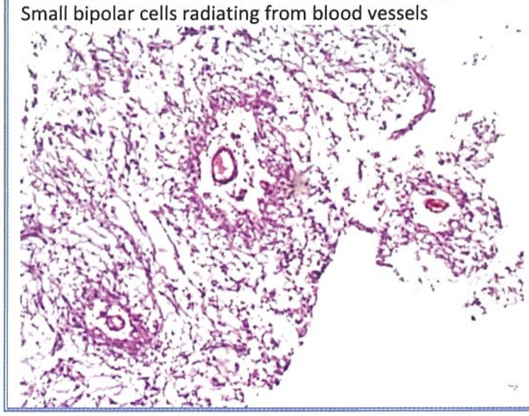
Loose myxoid background



Small bipolar cells radiating from blood vessels



PILOMYXOID ASTROCYTOMA (CNS WHO GRADE 2)

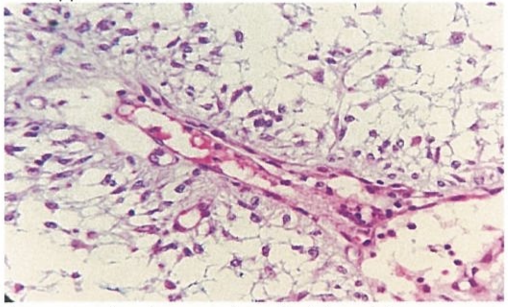
MORPHOLOGY

- Histologic **subtype of pilocytic astrocytoma**
- Composed of histologic features similar to classic pilocytic astrocytoma (diffuse myxoid background and monomorphic "piloid" cells) but differs in that it is **slightly more cellular**, contains a prominent angiocentric arrangement of tumor cells, and lacks **Rosenthal fibers and eosinophilic granular bodies**
- Gross exam: Solid to gelatinous lesion

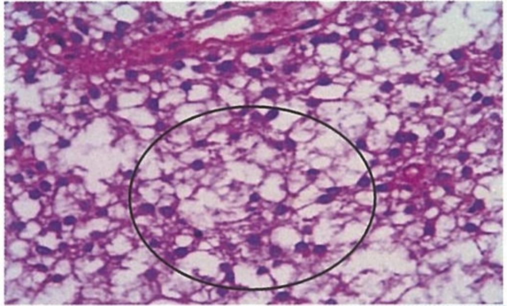
OTHER HIGH YIELD POINTS

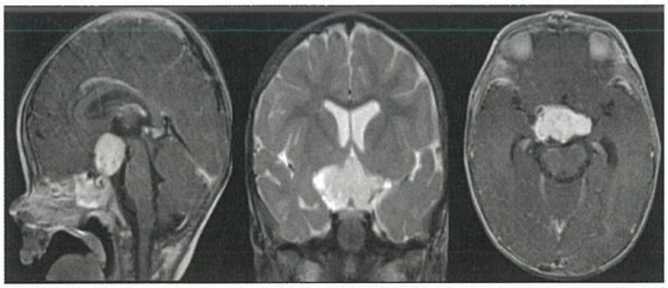
- Clinically presents with visual disturbance, hydrocephalus, polyuria, polydipsia, endocrine dysfunction, obesity, or proptosis
- Occurs in the hypothalamic/chiasmatic region; some cases have been reported in the cerebellum, brainstem, temporal lobe, and spinal cord
- Most common in children
- Higher rate of recurrence
- Propensity for cerebrospinal dissemination
- More likely to have necrosis
- Poorer prognosis than pilocytic astrocytoma
- IHC: (+) GFAP, S100, vimentin, synaptophysin (some cases), CD34 (some cases); (-) neurofilament, chromogranin; Ki-67: 2-20%
- Molecular: MAPK pathway gene alterations (similar to classic pilocytic astrocytoma)

Perivascular orientation of cells forming a "pseudorosette-like" appearance

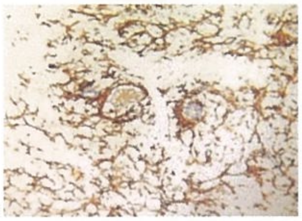


A very prominent mucopolysaccharide matrix

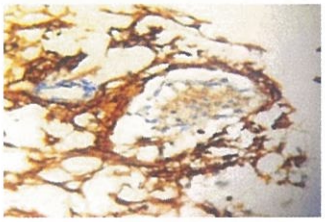




Pilomyxoid astrocytoma. Tumor in an 11-month-old girl. Sagittal, coronal, and axial MRI shows a tumor with solid and cystic characteristics extending to the optic chiasm
Picture courtesy: José A. Cortes, MD



GFAP



GFAP

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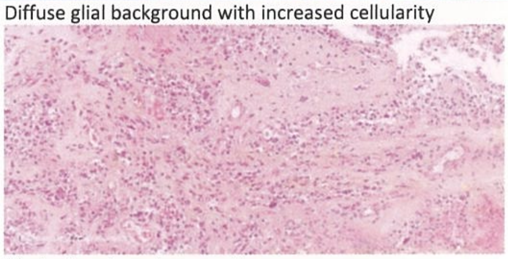
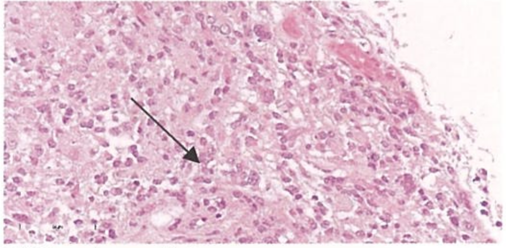
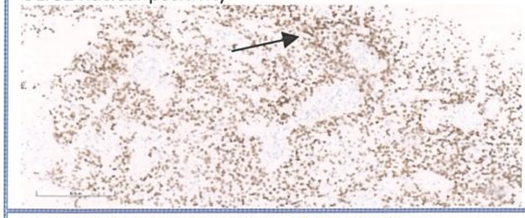
Diffuse glial background with increased cellularity



Marked nuclear pleomorphism



OLIG2 nuclear positivity



HIGH-GRADE ASTROCYTOMA WITH PILOID FEATURES (HGAP)

MORPHOLOGY

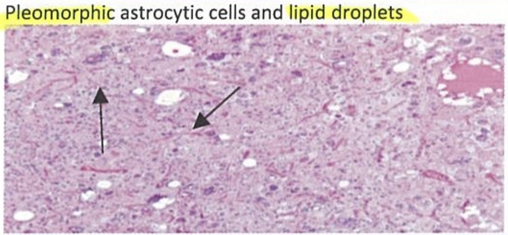
- Diffuse infiltrative high-grade astrocytoma with piloid and/or glioblastoma-like features with MAPK pathway alterations in combination with a homozygous deletion involving the CDKN2A and/or CDKN2B locus and/or ATRX mutation or loss of nuclear ATRX expression
- Glial element features: Thin, piloid cytoplasmic processes with a growth pattern similar to glioblastoma or pleomorphic xanthoastrocytoma; eosinophilic granular bodies, Rosenthal fibers
- Other features: Vascular glomeruloid proliferation, necrosis with or without palisading, and mitoses

OTHER HIGH YIELD POINTS

- Clinically, may vary according to the size and location of the tumor
- Occurs in the **cerebellum, cerebral hemispheres, and spinal regions**
- Occurs in patients ranging from 4-88 years;
- Risk factors: prior history of lower-grade astrocytoma, cerebral irradiation, or de novo
- **Poor prognosis**
- IHC: (-) ATRX (loss of expression); IDH1 R132H negative, H3 p.K28M (K27M)-mutant positive expression (rare)
- Molecular: MAPK pathway gene alteration, homozygous deletion or mutation of CDKN2A and/or CDKN2B, or amplification of CDK4, mutation of ATRX, or loss of nuclear ATRX expression

Pictures courtesy: Lakshmi Ramachandran Nair, MD

Pleomorphic astrocytic cells and lipid droplets

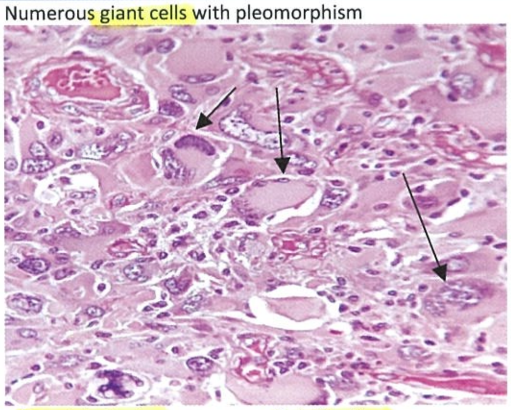


PLEOMORPHIC XANTHOASTROCYTOMA (CNS WHO GRADE 2-3)

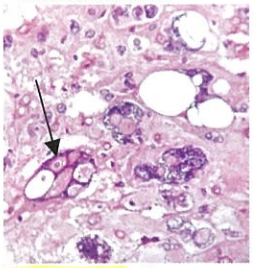
MORPHOLOGY

- Astrocytic neoplasm composed of large pleomorphic, spindled, and lipidized cells with numerous eosinophilic granular bodies, reticulin deposition, BRAF V600E mutation (or other MAPK pathway gene alterations), and homozygous CDKN2A and/or CDKN2B deletion
- Other features: Compact, lobulated, or fascicular architecture; may have pleomorphic multinucleated cells (astrocytes) with lipid droplets

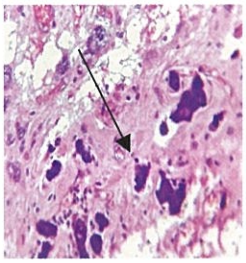
Numerous giant cells with pleomorphism



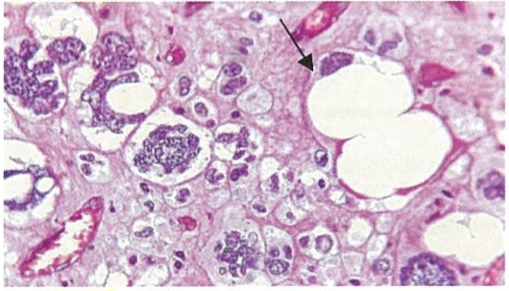
Pseudoinclusions



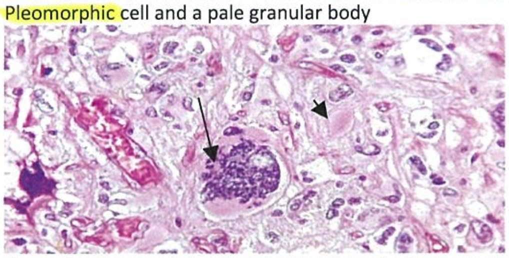
Calcifications



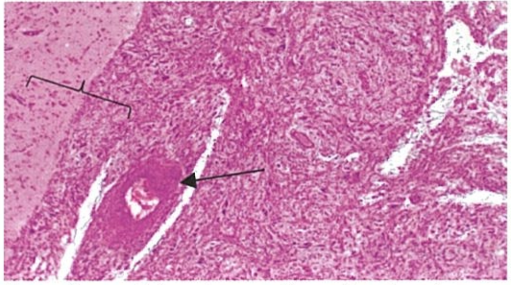
Xanthomatous changes



Pleomorphic cell and a pale granular body



Transitional zone with a well-defined tumor, gliosis, and an intratumoral artery with a hyalinized muscular wall



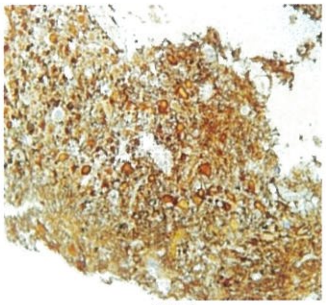
Areas of necrosis in a pleomorphic xanthoastrocytoma (grade 3)

(xanthomatous cells), epithelioid cells, intranuclear pseudoinclusions, prominent nucleoli, lymphocytic infiltration, granular bodies (pale and brightly eosinophilic), fibers that surround individual cells (common in leptomeninges), and vascular sclerosis; may have an anaplastic, small cell, fibrillary, or epithelioid/rhabdoid morphology

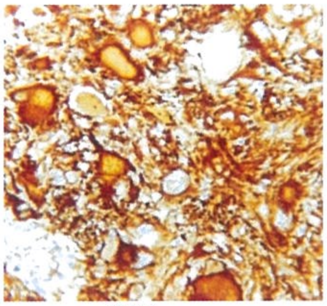
- **Grade 2**:
  - ➢ < 2.5 mitoses per mm^2 (equating to < 5 mitoses/10 HPF of 0.23 mm^2 in area and 0.54 mm in diameter)
  - ➢ Ki-67: < 1%
- **Grade 3**: May occur de novo or as a recurrence
  - ➢ Brisk mitotic activity (focal or diffuse)
  - ➢ > 2.5 mitoses per mm^2 (equating to > 5 mitoses/10 HPF of 0.23 mm^2 in area and 0.54 mm in diameter)
  - ➢ Necrosis
  - ➢ May demonstrate less pleomorphism and a more diffuse infiltrative pattern
  - ➢ Ki-67: Mean index is 15%
- Gross exam: Superficial, cortical, solid or cystic lesion with lipidization (yellow coloring)

OTHER HIGH YIELD POINTS

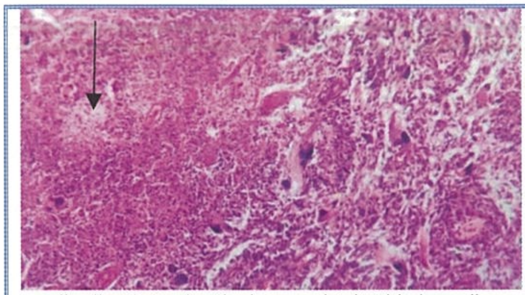
- Clinically presents with **a long history of seizures**; may vary according to size and location of tumor
- More commonly occurs supratentorially (98%) in a **superficial location of the temporal lobe**, involving the leptomeninges; may be present in the cerebellum and spinal cord
- Most common in the 1st-2nd decade; may affect older patients
- May be present in NF1 (MAPK pathway gene alterations), DiGeorge syndrome, familial melanoma-astrocytoma syndrome (CDKN2A inactivation), Down syndrome, and Sturge-Weber
- Imaging: CT scan with a variable appearance (hypodense, hyperdense, or mixed); hypointense or isointense, well-demarcated, solid or cystic lesion on T1-weighted MRI; hyperintense or mixed-signal cyst on T2-weighted MRI
- Recurrence, dissemination, and progression to grade 3 is common
- **IHC**: (+) BRAF V600E (VE1 antibody) in 60-80%; (+) **GFAP**, S100, **CD34**, synaptophysin, neurofilament (focally), class III beta tubulin, MAP2; SMARCB1 (INI1) focal loss (rarely)
- Molecular: **BRAF mutation or other MAPK pathway gene alterations in combination with homozygous deletion of CDKN2A and/or CDKN2B**



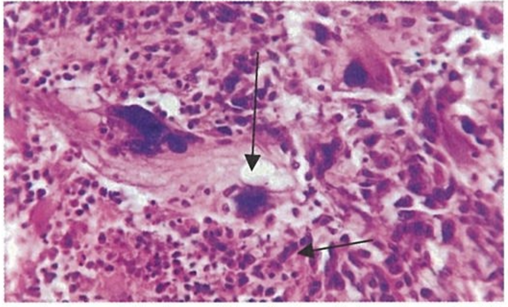
GFAP



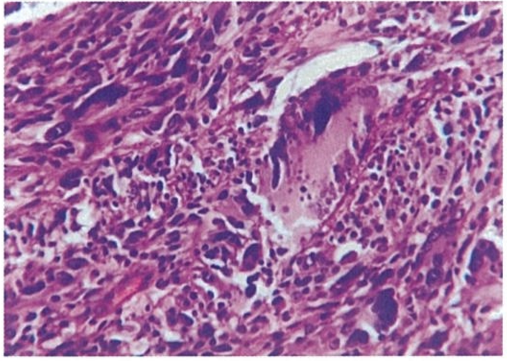
GFAP



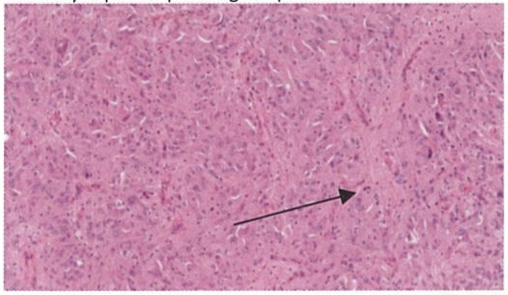
Small cells admixed with pleomorphic lipid-laden cells



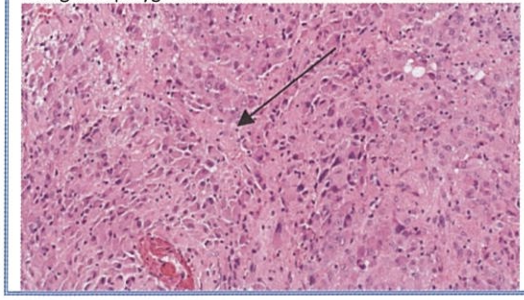
Fascicular architecture with spindle cells in a pleomorphic xanthoastrocytoma (grade 3)

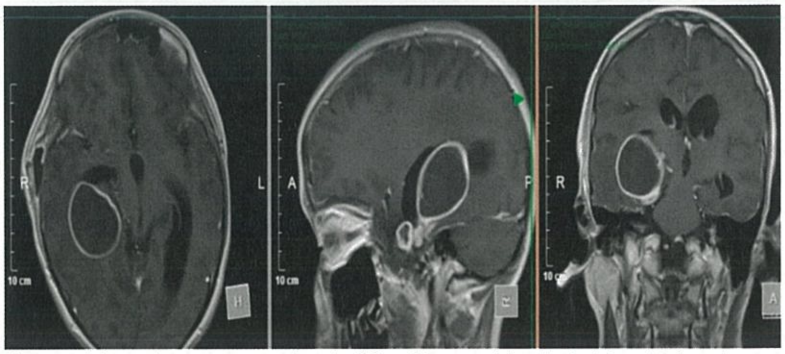


Fibrillary septae separating neoplastic cells



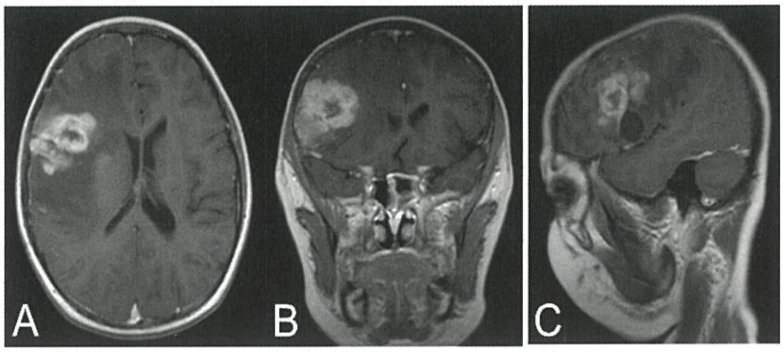
Elongated polygonal cells





Pleomorphic xanthoastrocytoma (grade 2) in a 13-year-old male. Axial, sagittal, and coronal MRI showing a well-circumscribed lesion with ring enhancement in the right temporal lobe

Picture courtesy: José R. Cortez, MD and Hector Hernandez, MD



Pleomorphic xanthoastrocytoma (grade 3) in a 10-year-old male. Axial, coronal, and sagittal MRI shows a superficial tumor with solid-cystic areas and necrosis

Picture courtesy: Victor Romero, MD and Hernan Leyva, MD

Path Presenter

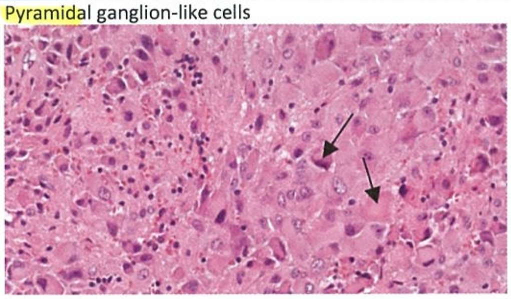
Path Presenter

SUBEPENDYMAL GIANT CELL ASTROCYTOMA (SEGA) (CNS WHO GRADE 1)

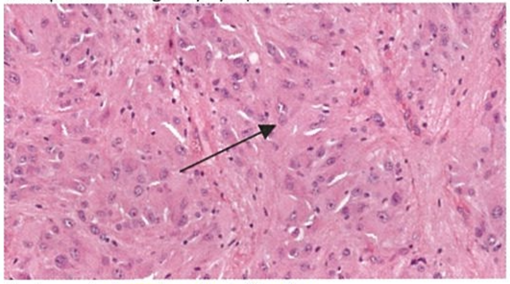
MORPHOLOGY

- Astrocytic periventricular neoplasm composed of large ganglion-like cells that are associated with tuberous sclerosis (TS)
- Glial features: May have a broad spectrum of glial phenotypes (typical polygonal cells with abundant glassy cytoplasm, smaller spindle cells, or gemistocyte-like cells arranged in fascicles, sheets, or nests with intervening fibrillary septae)
- Other features: Giant pyramidal-like cells with a ganglionic appearance that have eccentric, vesicular nuclei with distinct nucleoli and no Nissl substance; nuclear inclusions, pleomorphism, and multinucleated cells; clustering of tumor cells and a perivascular rosette-like pattern (resembles ependymoma); rich vascular stroma with hyalinized vessels; infiltration of mast cells and lymphocytes; parenchymal or vascular calcifications
- **Some cases may have mitoses, vascular proliferation, or necrosis, but this does not indicate anaplastic progression**
- Gross exam: SEGAs may be multinodular, sharply demarcated, white, solid lesions with cystic degeneration (in some cases); subependymal nodules (SENs) may be small, nodular lesions attached to the ventricle lining
- SEGAs: > 5 mm
- SENs: < 5 mm

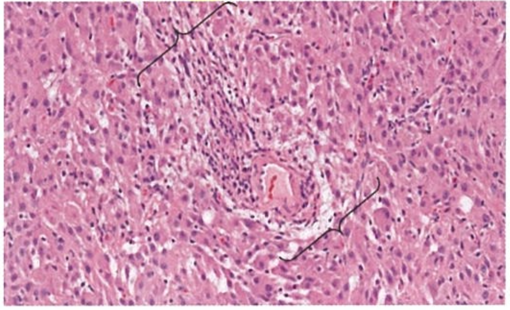
Pyramidal ganglion-like cells



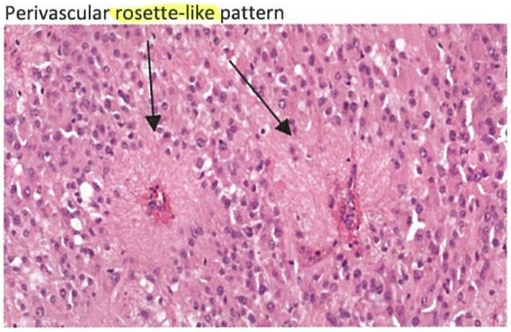
Plump cells with glassy cytoplasm and eccentric nuclei



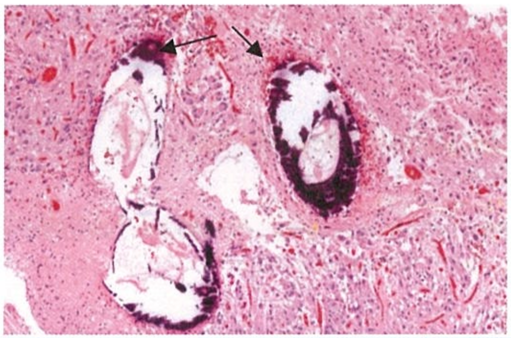
Perivascular lymphocytic infiltration



Perivascular rosette-like pattern

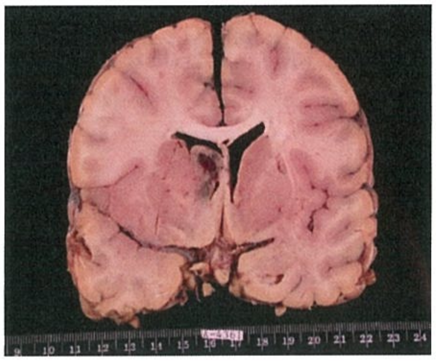


Areas with many vascular calcifications

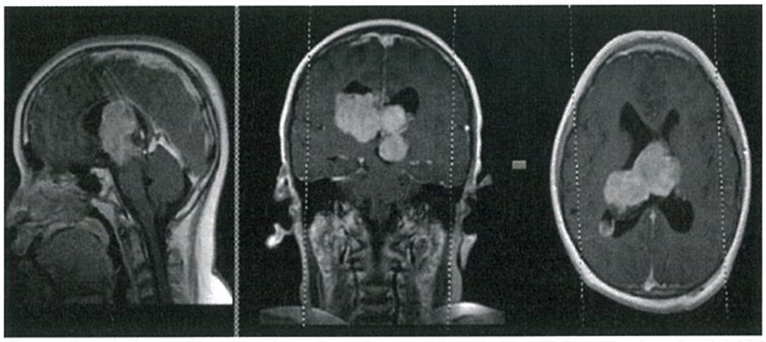


OTHER HIGH YIELD POINTS

- Clinically presents with **hydrocephalus**, signs and symptoms of increased intracranial pressure, and a **long history of seizures**; acute presentation may be massive spontaneous hemorrhage
- Associated with inherited TS
- More commonly occurs in the lateral ventricles adjacent to the foramen of Monro; may arise in the 3rd ventricle and retina
- Most common in the 1st-2nd decade; may arise de novo in older patients (20-25 years)
- SENs may grow into SEGAs within the first 2 decades of life
- Imaging: Heterogeneous, isointense, or slightly hypointense solid lesion on T1-weighted MRI; T2-hyperintense with marked contrast enhancement and ipsilateral or bilateral ventricular enlargement
- Proton magnetic resonance spectroscopy may be a valuable tool for early detection of transformation from SEN to SEGA, showing a high ratio of choline to creatinine and a low ratio of N-acetylaspartate to creatinine
- Favorable prognosis with total tumor resection; surveillance by MRI every 1-3 years until the age of 25 for patients with TS
- IHC: (+) GFAP, TTF1, S100, synaptophysin, NeuN, neuropeptides, nestin, SOX2, class III beta tubulin
- Hamartin and tuberin loss
- Molecular: **TSC1 or TSC2 mutation;** has a distinct DNA methylation profile



Subependymal giant cell astrocytoma in a 33-year-old female with TS. Coronal section shows a whitish-gray lesion in the left ventricle
Picture courtesy: Dr. Luis A. Cecenas, MD



Subependymal giant cell astrocytoma in a 7-year-old male. Sagittal, coronal, and axial MRI showing a bulky, contrast-enhancing mass in the region of the foramen of Monro
Picture courtesy: Victor Romero, MD and Louis V. Carius, MD

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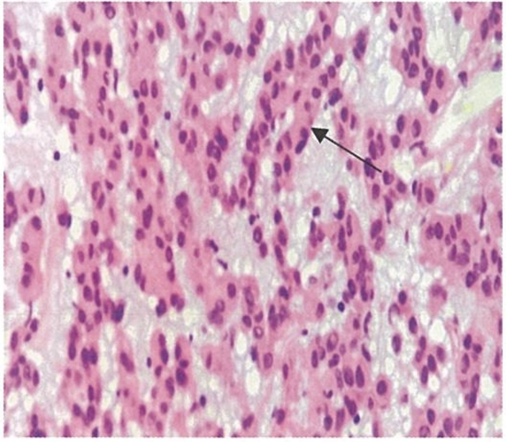
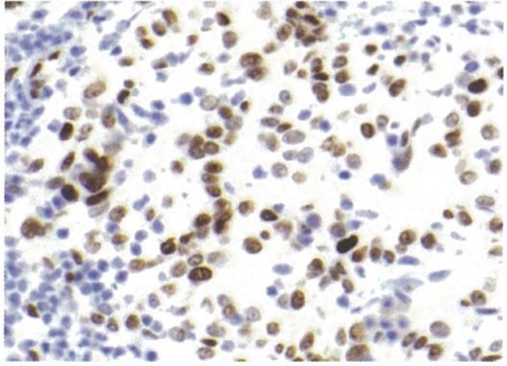
Cords of neoplastic cells in variable mucinous stroma
Picture courtesy: Simon Roy, MD



Strong nuclear positivity: TTF1
Picture courtesy: Mireille Bitar, MD



CHORDOID GLIOMA (CNS WHO GRADE 2)

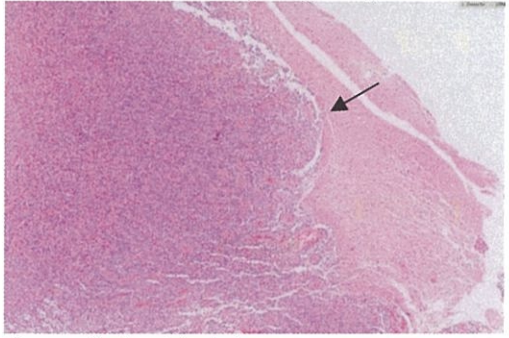
MORPHOLOGY

- Glial tumor arising in the 3rd ventricle that is composed of epithelioid cells disposed in clusters and cords expressing GFAP
- Glial element features: Individual cells have abundant eosinophilic cytoplasm with moderate-sized, ovoid, relatively uniform nuclei
- 3 morphologic patterns:
  - Solid pattern: Sheets of polygonal epithelioid cells without mucinous stroma
  - Fusiform pattern: Groups of spindle-shaped cells among loose collagen
  - Fibrosing pattern
- Other features: Stromal lymphoplasmacytic infiltrate that may commonly contain Russell bodies; adjacent to the tumor-reactive astrocytes, Rosenthal fibers and chronic inflammatory cells may be seen
- Gross exam: Well-demarcated but often multilobulated soft, gray, gelatinous lesions

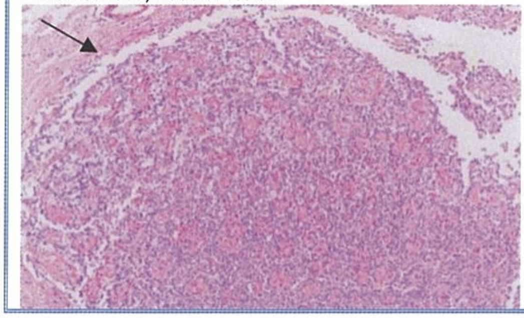
OTHER HIGH YIELD POINTS

- Clinically presents with **signs and symptoms of obstructive hydrocephalus** (headaches, nausea, and vomiting) or ataxia; may present with **endocrine abnormalities** due to hypothalamic compression (hypothyroidism, amenorrhea, diabetes insipidus); **visual field disturbances** due to compression of the optic chiasm and **psychiatric symptoms**
- Occurs in the anterior portion (lamina terminalis) of the **3rd ventricle**
- Most common in adults (median: 45 years) with a female predominance of 1:2)
- Imaging: T1-isointense, well-demarcated, solid, ovoid, multilobulated lesion; may have an anterior hypothalamic component
- Recurrence uncommon, with an **excellent prognosis**
- IHC: (+) GFAP, TTF1, CD34, vimentin; S100 and EMA variable expression; Ki-67 proliferation index usually < 2%
- Molecular: **PRKCA p.D463 mutation** or DNA methylation profile for chordoid glioma

Well-defined borders with "pushing" margins



Circumscribed, nodular lesion



ASTROBLASTOMA, MN1-ALTERED (NOT CURRENTLY GRADED)

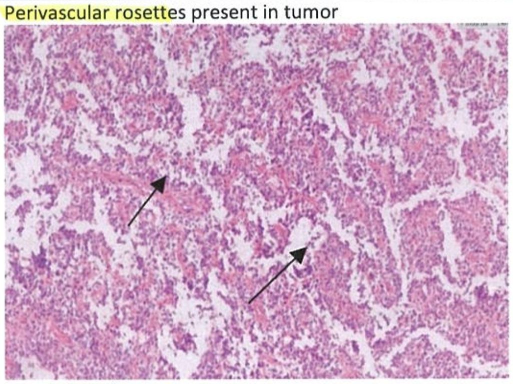
MORPHOLOGY

- Well-circumscribed glial neoplasm composed of round, cuboidal, or columnar cells with variable pseudopapillary or perivascular growth and MN1 alteration
- Glial element features: Neoplastic cells that are classically elongated or stout with eosinophilic cytoplasm and nuclei oriented distally, away from the pseudorosette center
- These cells are radially arrayed around blood vessels, often forming papillary or pseudopapillary structures in cross-sections and regimented, ribbon-like/trabecular alignment in tangential views known as **astroblastic pseudorosettes**
- Other features: Vascular and stromal sclerosis with extended regions of hyalinization that contain a few remnants of tumor cells in cords
- Gross exam: Well-delineated, grayish-pink, solid or cystic lesion that may have necrosis and hemorrhage

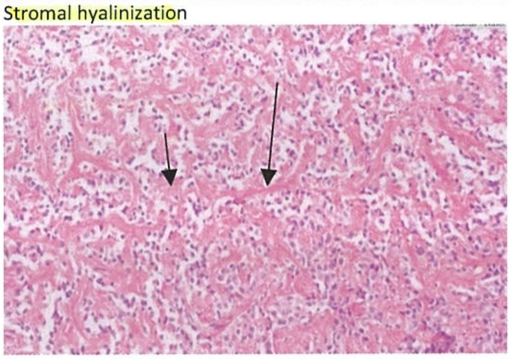
OTHER HIGH YIELD POINTS

- Clinically presents with seizures, paralysis, and intracranial pressure symptoms such as headaches, nausea, and vomiting
- More frequently occurs in the **frontal and parietal lobes**; may also be intraventricular or present in other lobes, the brainstem, or the spinal cord
- Most common in the 1st-4th decades (median: 15 years) with female predominance

Perivascular rosettes present in tumor



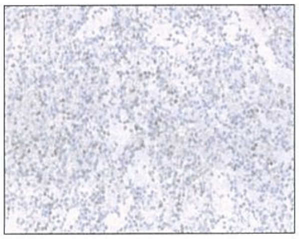
Stromal hyalinization



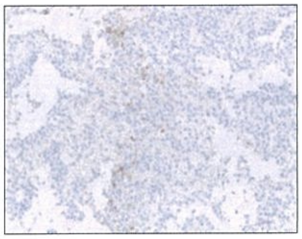
Astroblastoma, MN1-altered in a young adult female
Pictures courtesy: Felipe D´Almeida Costa, MD

- Imaging: Hypointense or isointense, well-demarcated, solid or cystic lesion on T1-weighted MRI; T2-hyperintense with heterogeneous contrast enhancement and perilesional edema
- Overall survival prognosis is good, although associated with local recurrence; in tumors with high-grade histology, a worse prognosis has been reported
- IHC: (+) GFAP, OLIG2 (focal), EMA (diffuse, membranous, dot-like/ring-like), D2-40; Ki-67 variable
- Molecular: Rearrangement of the MN1 gene at chromosome band 22q12.1.MN1 fusions which most often occur in frame with BEND2 at chromosome band Xp22.13; some tumors may have CDKN2A homozygous deletion; DNA methylation profile of astroblastoma, MN1-altered

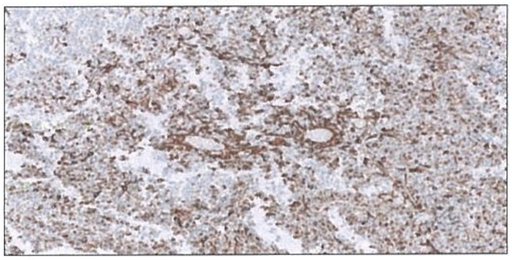
OLIG2 shows focal nuclear positivity



EMA shows dot-like positivity



GFAP



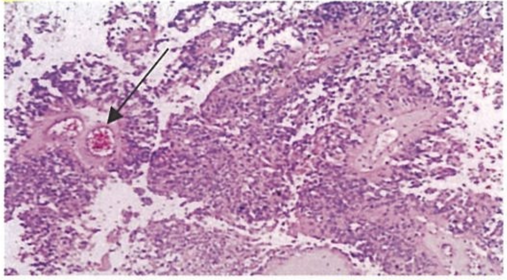
CLASSIFICATION OF EPENDYMAL TUMORS

SUPRATENTORIAL EPENDYMOMA	**ZFTA (C11orf95) FUSION-POSITIVE** All ages Intermediate prognosis IHC (+) L1CAM CDKN2A/B loss Chromothripsis	**YAP1 FUSION-POSITIVE** Infants and children Good prognosis
POSTERIOR FOSSA EPENDYMOMA	**GROUP A (PFA)** Infants and children Poor prognosis EZHIP or H3 K27M mutation IHC: Loss of H3 K27me3 nuclear staining Chromosome 1q gain	**GROUP B (PFB)** Children < adults Good prognosis IHC: Retained nuclear H3 K27me3 Chromosomal instability
SPINAL EPENDYMOMA	**SPINAL EPENDYMOMA** Adults Intermediate prognosis NF2 mutations Loss of chromosome 22 Absence of MYCN amplification	**MYCN-AMPLIFIED** Children and adults Poor prognosis Usually cervical or thoracic spinal cord High-grade histology usually present Frequent CSF dissemination

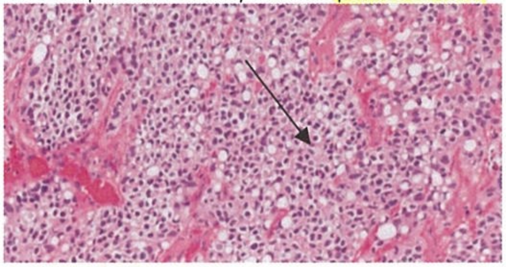
10. GLIAL TUMORS

EPENDYMAL TUMORS

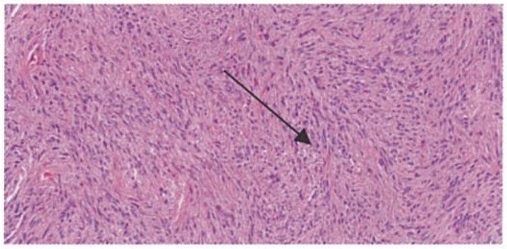
"Classic/cellular" features with perivascular pseudorosettes



Clear cell pattern formed by cells with perinuclear halos



Tanycytic pattern formed by spindle cells arranged in fascicles



GENERAL FEATURES

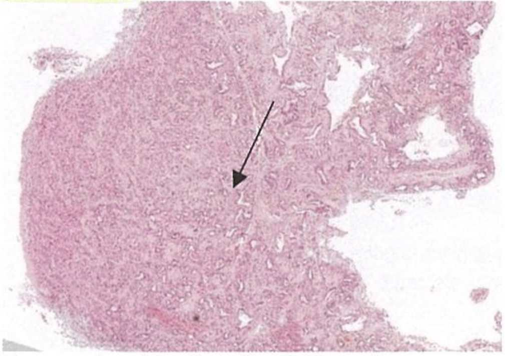
MORPHOLOGY

- Circumscribed gliomas composed of uniform small cells with round nuclei and speckled chromatin in a fibrillary matrix
- Characteristic **perivascular pseudorosettes** (perivascular anucleated zones)
- True ependymal rosettes found in a minority of cases
- Specific morphologic patterns (CNS 5 WHO classification)
  - Cellular: Solid growth pattern with perivascular pseudorosettes
  - Clear cell: More common in supratentorial ependymoma
  - Papillary: More common in posterior fossa ependymoma
  - Tanycytic (spindle cells): More common in spinal ependymoma

OTHER HIGH YIELD POINTS

- Classification based on anatomic location, histomorphology, and molecular features
- **Grade 2**:
  - Mild to moderate cellularity and nuclear atypia
  - Well-differentiated fibrillary background
- **Grade 3:**
  - Moderate to marked cellularity with increasing nuclear atypia
  - **Microvascular proliferation**
  - **Brisk mitotic activity**
- Histologic grade (CNS WHO grades 2-3) does not consistently correlate with tumor behavior and prognosis
- IHC: (+) GFAP, **EMA (perinuclear, dot-like pattern)**
- Spinal ependymoma generally shows loss of chromosome 22 and is associated with neurofibromatosis type 2 (NF2)

Nodular areas showing true ependymal rosettes and pseudorosettes



True ependymal rosettes with columnar cells

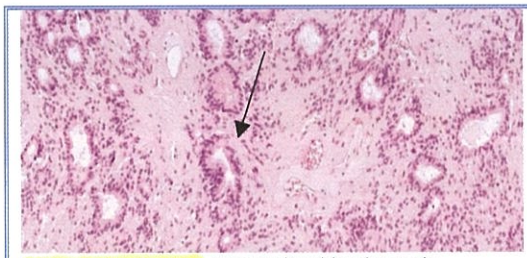
SUPRATENTORIAL EPENDYMOMA, ZFTA FUSION-POSITIVE AND YAP1 FUSION-POSITIVE (CNS WHO GRADES 2-3)

MORPHOLOGY

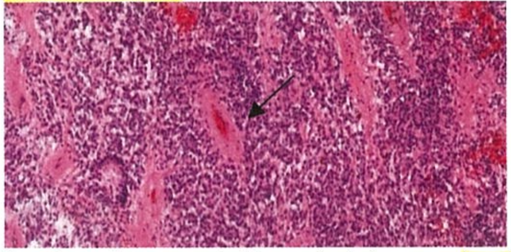
- Heterogeneous histopathologic features with pseudorosettes and true ependymal rosettes variably present
- Sharp interface with adjacent glial parenchyma
- Mild nuclear pleomorphism may be seen
- Mitotic count is variable
- Other features: Clear cell changes (oligodendroglioma-like), prominent vasculature with a branching network pattern (capillary blood vessels), hyalinized blood vessels, and calcifications
- Gross exam: Soft, tan, with spongy or gritty appearance

OTHER HIGH YIELD POINTS

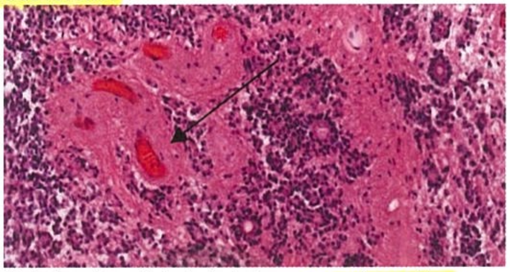
- Clinically presents with seizures, focal neurologic deficits, hydrocephalus, headaches, nausea, and vomiting
- Most common in the **frontal** and parietal lobes; may be present in other lobes (temporal and occipital) and **may not show an obvious connection with the ventricular system**
- Most common in the 1st-2nd decades but can occur at any age
- Imaging: MRI with heterogeneous, contrast-enhancing lesions containing solid or partially cystic components



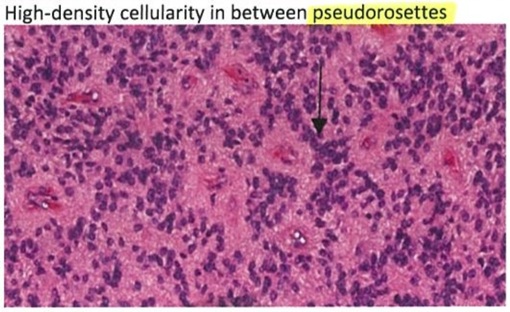
Perivascular rosettes surrounding blood vessels



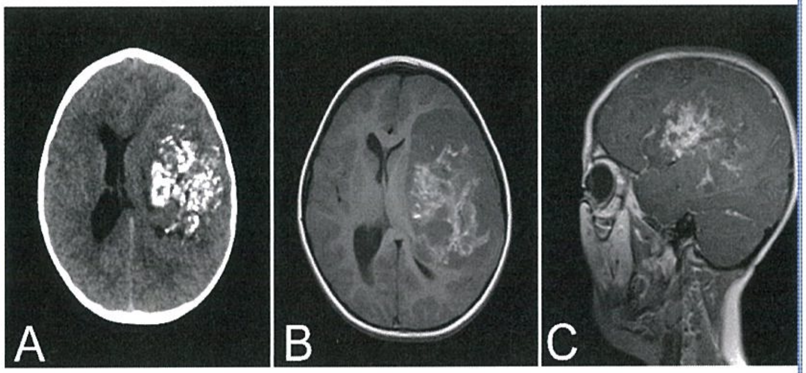
Pseudorosettes surrounded by anucleated zones and small true rosettes



High-density cellularity in between pseudorosettes



- Poor prognosis
- IHC:
  - (+) GFAP, EMA
  - p65 and L1CAM positive for ZFTA RELA-fused ependymoma and negative for YAP1-fused ependymoma
- Molecular: ZFTA (C11orf95) gene fusion with RELA; YAP1 gene fusion with MAMLD1; DNA methylation profile of supratentorial ependymoma, ZFTA fusion-positive or YAP1 fusion-positive



Ependymoma in a 3-year-old male. A. Axial CT scan with an intraaxial, solid, heterogeneous tumor with calcifications and a necrotic center (**periwinkle sign**)
B. T1-weighted axial section with a solid, hypointense tumor
C. T1-weighted MRI with contrast enhancement, edema, and mass effect
Picture courtesy: José R. Cortes, MD, Juan F. Tovar, MD, and Silvia Alvarez, MD

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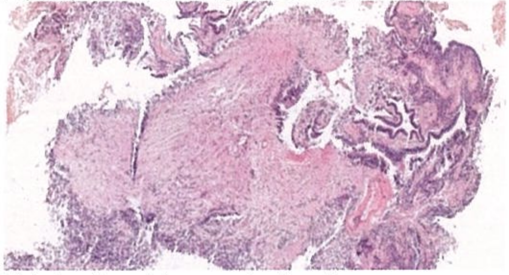
Papillary structures emerging from a glial component



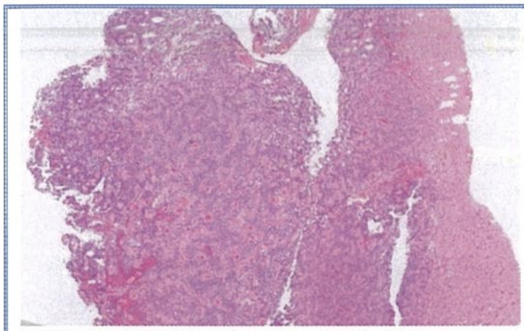
High-density nodules emerging from the pons

POSTERIOR FOSSA EPENDYMOMA GROUP A (PFA) and GROUP B (PFB) (CNS WHO GRADES 2-3)

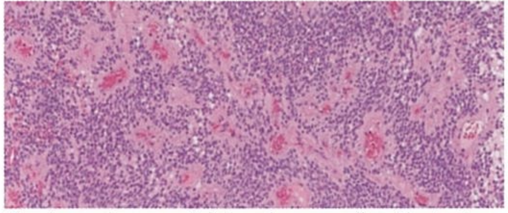
MORPHOLOGY

- Heterogeneous histopathologic features with pseudorosettes (almost always present) and true ependymal rosettes (present in few cases)
- High-density cellularity forming nodular-like areas
- Mild nuclear pleomorphism may be seen
- Mitotic count is variable
- Architecture containing finger-like projections (papillary or pseudopapillary)
- Other features: Microcystic changes, hyalinization of blood vessels, calcifications, cartilaginous or osseous metaplasia (rarely)
- Gross exam: Soft and tan with a spongy or gritty appearance; may extend through the foramina of Luschka and envelop the lower cranial nerves and the posterior inferior cerebellar artery

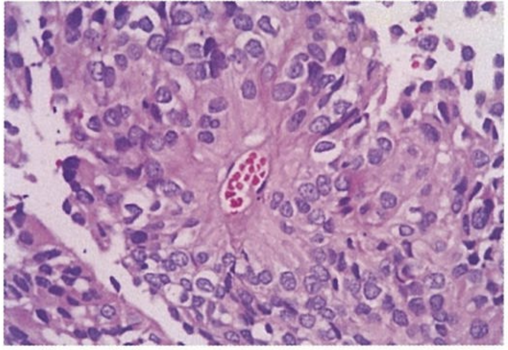
OTHER HIGH YIELD POINTS



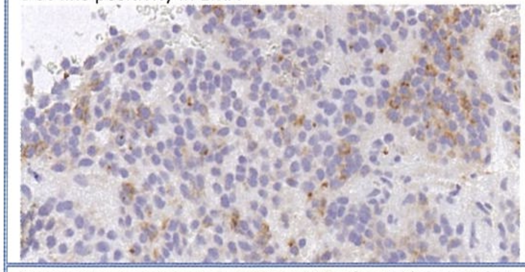
Many pseudorosettes in a perivascular fashion



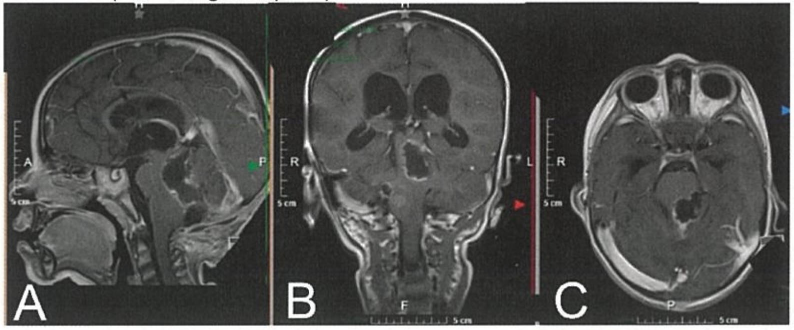
Blood vessel surrounded by columnar cells with atypia



Dot-like positivity in EMA



- Clinically presents with hydrocephalus, headaches, nausea, vomiting, and large head circumference (younger children)
- Most common in the **4th ventricle** and cerebellopontine angle
- Most common in the 1st decade (median age at 6 years) but can occur at any age; slight male predominance (in general)
- IHC: (+) GFAP, S100, EMA, CK7 (focal), CK20 (focal); (-) OLIG2
- Posterior fossa group A:
  - < 6 years of age (mean is 3 years)
  - Arises in roof and lateral aspect of the 4th ventricle
  - Slight male predominance
  - IHC: H3 p.K28me3 (K27me) (global reduction)
  - DNA methylation profile for posterior fossa group A
- Posterior fossa group B:
  - Occurs in adults and adolescents (rarely in children)
  - Arises in the floor of the 4th ventricle
  - Slight female predominance (PFB-3 and PFB-5)
  - IHC: H3 p.K28me3 (K27me) (retained)
  - DNA methylation profile for posterior fossa group B
  - PFB-1, PFB-2, PFB-3 in patients 25-30 years; PFB-4 (median age: 15 years); PFB-5 (median age: 40 years)



A, B, C. Sagittal, coronal, and axial T1-weighted MRI showing a solid-cystic lesion with peripheral contrast enhancement in the 4th ventricle with extension to the basal cisternae, mass effect, and supratentorial hydrocephalus
Picture courtesy: José R. Cortes, MD and Silvia Alvarez, MD

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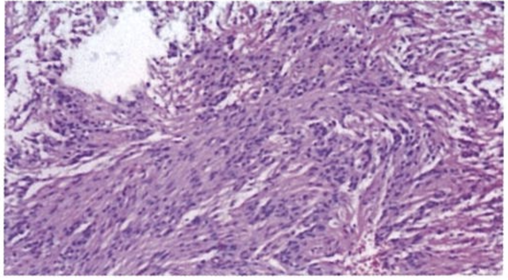
Tanycytic ependymoma arranged in a fascicular manner



SPINAL EPENDYMOMA, (CNS WHO GRADES 2-3)

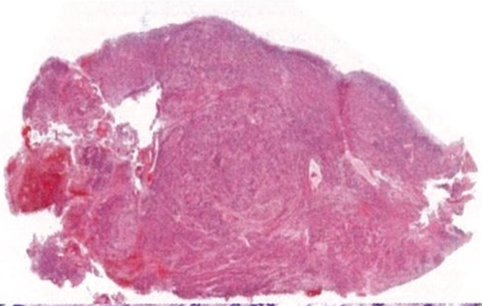
MORPHOLOGY

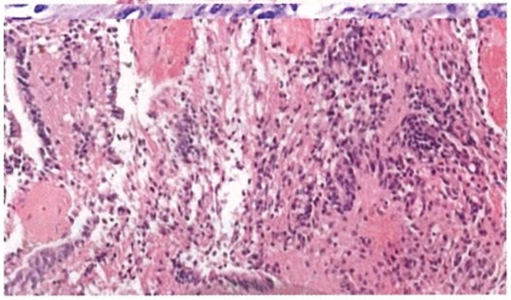
- Histopathologic features with pseudorosettes (most cases) and true ependymal rosettes (few cases)
- Tanycytic pattern with prominent spindle-shaped cells and bipolar processes
- Absence of myxopapillary ependymoma or subependymoma
- Low mitotic count (most cases)
- Other features: Dense collagenous nodules, hemorrhage, necrosis, calcifications, cystic changes, cartilage metaplasia, and myxoid or bone degeneration

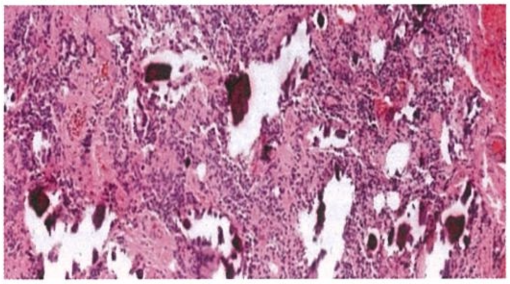
OTHER HIGH YIELD POINTS

- Clinically presents with pain, motor, and sensory deficits
- Most common in cervical or cervicothoracic regions
- Most common in adults between 25-45 years but can occur at any age
- Association with NF2

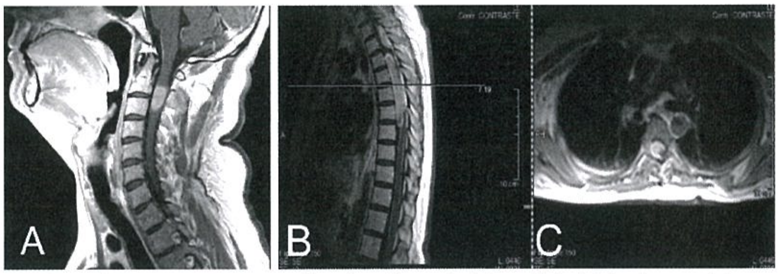
Elongated cells that cluster in a fibrillary background
Panoramic view of the tumor
Papillary structures and elongated nuclei
Many areas of calcification within the tumor cells







- Imaging: MRI with intramedullary, contrast-enhancing lesion; T1-weighted images are hypointense and T2-weighted images are hyperintense
- Overall good prognosis if total resection is done
- IHC: (+) GFAP, S100, vimentin, EMA (dot-like); (-) OLIG2, SOX10
- Molecular: DNA methylation profile of spinal ependymoma, loss of chromosome 22q; absence of MYCN amplification (most common)
  - Spinal ependymoma, MYCN-amplified (high-grade features, no WHO grade assigned yet, few cases reported, worse prognosis)



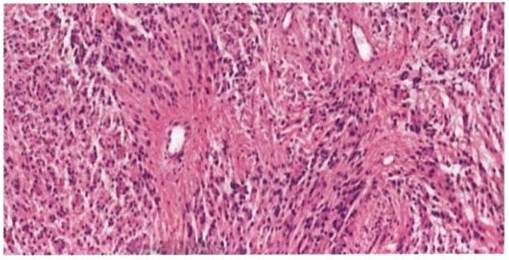
Spinal ependymoma in a 38-year-old male with cervicalgia and diminished strength in upper extremities. A. Sagittal T1-weighted MRI showing a solid-round area of contrast enhancement in an intramedullary cervical tumor

B. Sagittal T1-weighted MRI showing a solid-oval, contrast-enhanced, intramedullary thoracic tumor

C. Axial MRI with a contrast-enhancing lesion in the thoracic region

Picture courtesy: Rosalba Bustos, MD, Carlos Hernandez-Choel, MD, and Vicente Estrada, MD

Elongation of cells around anuclear zones and vascular spaces



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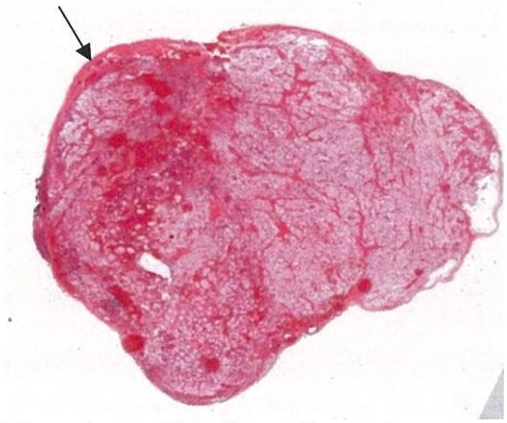
A small, delicate, encapsulated tumor

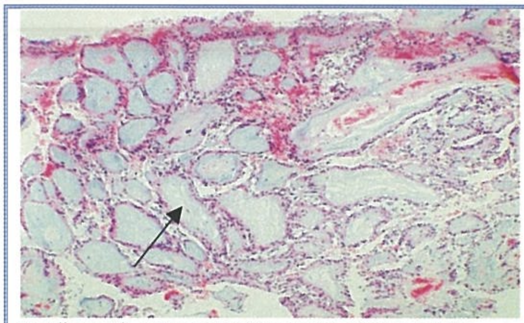


Microcystic areas filled with myxoid material

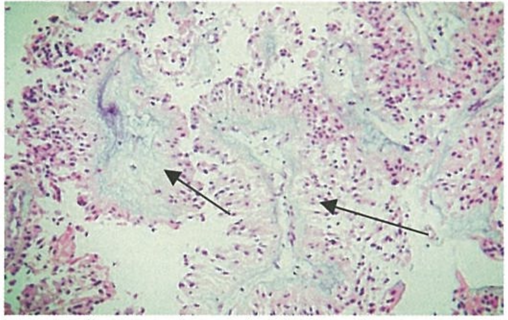
MYXOPAPILLARY EPENDYMOMA (CNS WHO GRADE 2)

MORPHOLOGY

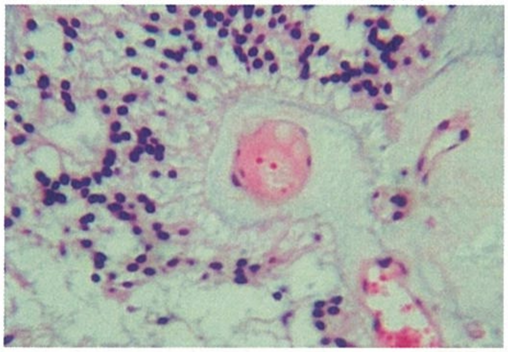
- Glial neoplasm composed of cuboidal-columnar (epithelial) cells or elongated and spindled (glial) cells arranged radially around hyalinized fibrovascular cores with microcystic formation and perivascular myxoid changes
- May form papillary-like structures or confluent solid sheets
- Myxoid material is present around blood vessels, in microcysts, or as extensive extravascular pools
- PAS-positive, eosinophilic spherules (balloons) that appear to have a prickly appearance in reticulin stains may be present in more solid tumors
- Other features: Fibrosis, collagenization, hemorrhage, and hemosiderin deposits
- "Anaplastic" myxopapillary ependymoma (grade 3) (exceptional cases)
  - Regional hypercellularity
  - Reduced mucin
- And **at least 2** of the following features:
  - Greater than or equal to 2 mitoses/mm^2
  - Ki-67 greater than or equal to 10%



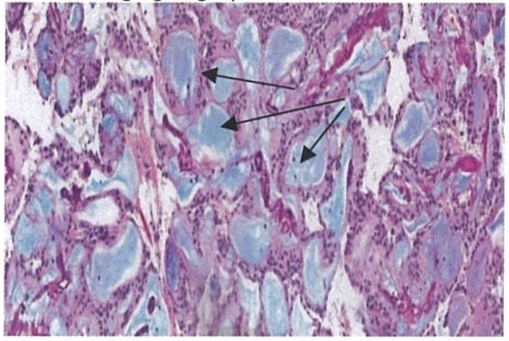
Papillae with scarce myxoid material surrounded by elongated cells



Tumor cells oriented toward a fibrovascular core



Alcian blue highlighting myxoid content

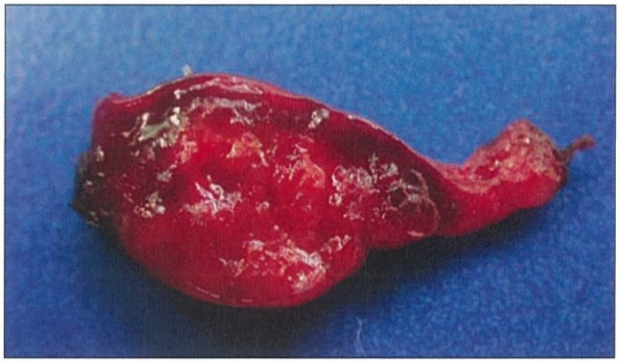


Strong GFAP immunoreactivity in tumor cells

  - ➢ Microvascular proliferation
  - ➢ Spontaneous necrosis
- Gross exam: Well-encapsulated, elongated, "sausage-like", soft to gelatinous pink-gray tumor

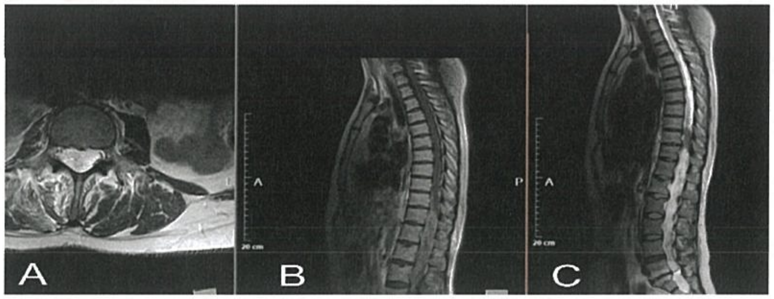
OTHER HIGH YIELD POINTS

- Clinically presents with cauda equina syndrome, pain, sensorimotor deficits, sciatica, impotence, and sphincter dysfunction
- Most commonly and almost exclusively occurs in the conus medullaris and filum terminale; other rare reported locations include the cervicothoracic spine, lateral ventricles, 4th ventricle, and brain
- Most commonly affects adults with 2 peaks at 25-29 years and 45-59 years; may occur in children and adolescents
- Imaging: MRI with contrast-enhancing, solid, sharply circumscribed tumor; may have a partially cystic component and hemorrhage
- Overall favorable prognosis; if not removed completely, may grow locally and/or have cerebrospinal fluid-borne seeding
- IHC: (+) GFAP (diffusely), S100, CD99, CD56, AE1/AE3 pancytokeratin cocktail; (-) EMA, OLIG2
- PAS and Alcian blue stains highlight myxoid material
- Molecular: DNA methylation profile of myxopapillary ependymoma



Myxopapillary ependymoma. Well-encapsulated, soft, pink-tan tumor with a "sausage-like" appearance

Picture courtesy: Silvia J. Hernandez, MD

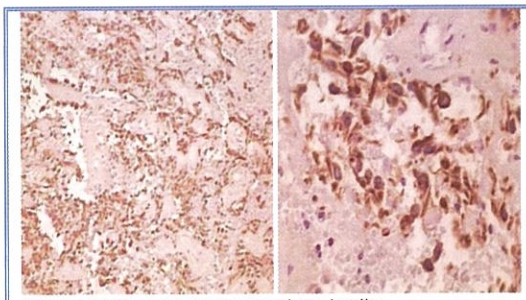


Myxopapillary ependymoma in a 43-year-old female with decreased lower extremity strength and paresthesia.

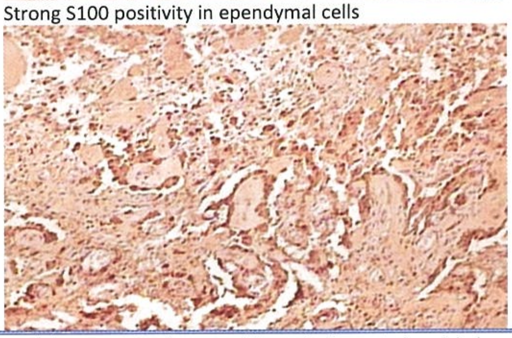
A. Axial T2-weighted MRI showing a heterogeneous intramedullary lesion

B. Sagittal T1-weighted MRI with contrast-enhanced lesion

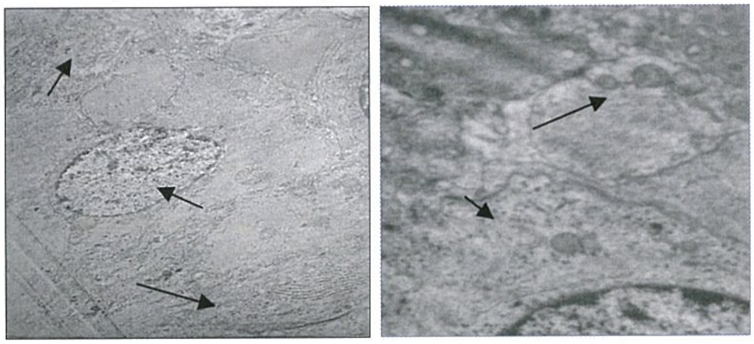
C. Sagittal T2-weighted MRI with a hyperintense lesion



Strong S100 positivity in ependymal cells



Picture courtesy: José Garcia de la Rosa, MD and Kevin Frias, MD



Myxopapillary ependymoma. Electron microscopy shows ultrastructural features with interdigitating cell processes, cellular elongations, and a regular nucleus with dispersed chromatin in the 1st image. The 2nd image shows microtubular aggregates within the rough endoplasmic reticulum

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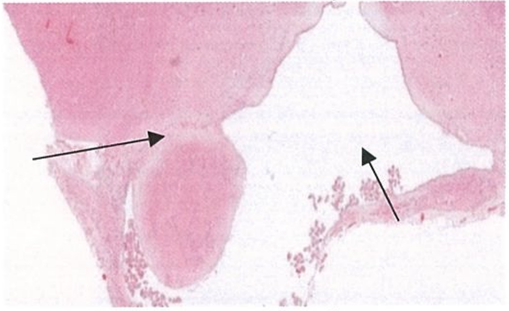
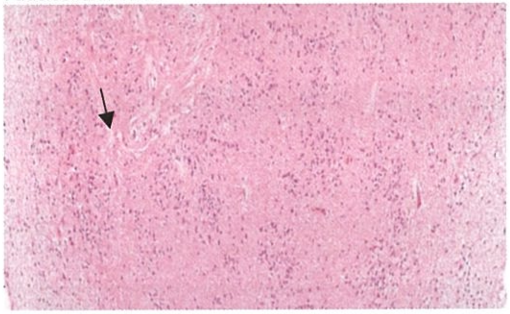
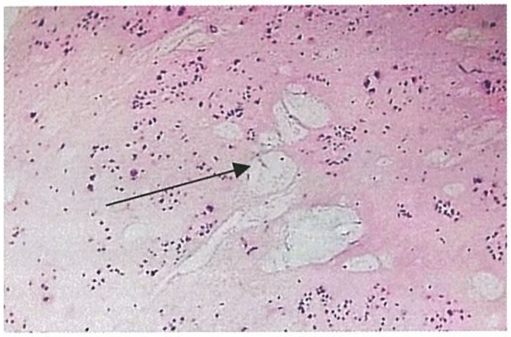
Nodular tumor in the ventricle and adjacent choroid plexus



Paucicellular tumor with scattered cells



Prominent microcystic changes



Glial background with grouped cells

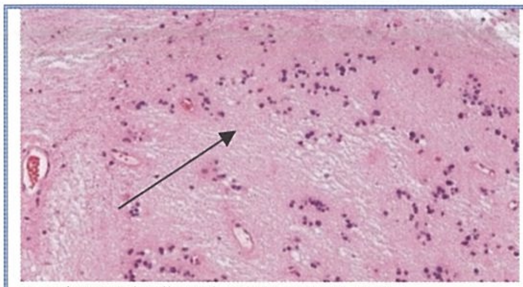
SUBEPENDYMOMA (CNS WHO GRADE 2)

MORPHOLOGY

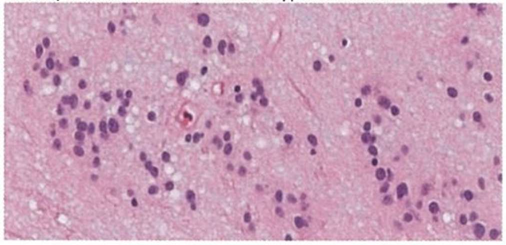
- Glial tumor composed of cells that are uniform to pleomorphic and are clustered like "bundles of flowers" embedded in a fibrillary matrix that may have microcystic changes (especially in the lateral ventricles)
- Other features: Prominent sclerotic or ectatic microvasculature, calcifications, nuclear pleomorphism, focal perivascular pseudorosettes (rare cases), low mitotic rate, non-palisading necrosis, hemosiderin deposition, melanotic pigmentation, and sarcomatous changes
- Gross exam: Well-delineated, solid or cystic lesion with calcifications

OTHER HIGH YIELD POINTS

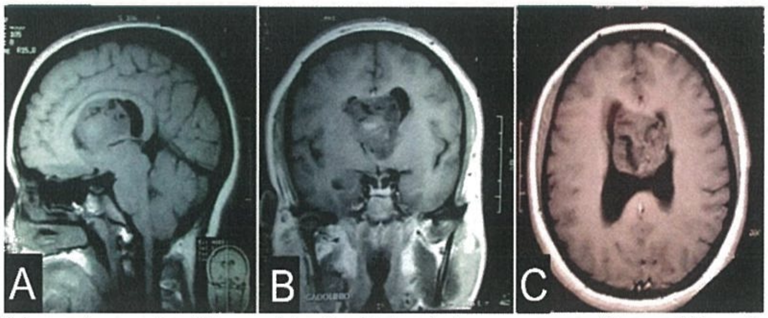
- Usually asymptomatic; symptoms may include headaches, nausea, and vomiting
- 50-60% occur in the 4th ventricle; may be present in lateral ventricles in 30-35%, 3rd ventricle, and spinal cord (cervicothoracic regions) as eccentric lesion; rarely seen in cerebral hemispheres, cerebellum, bulbar region, and cerebellopontine angle
- < 1% of intracranial neoplasms; most common around the 4th-8th decades with a slight male predominance
- Imaging: T1-hypointense, well-demarcated, solid lesion; T2-hyperintense with cystic changes, calcifications, and focal areas with contrast enhancement
- Recurrence is uncommon; excellent prognosis
- IHC:
  - Glial markers: (+) GFAP, OLIG2 (occasionally)
  - (+) EMA (dot-like)
  - Synaptophysin, SOX10, TOP2B, MDM2, nucleolin, phosphorylated STAT3, aquaporin-1 and aquaporin-4 (rarely positive)
  - (-) IDH1 R132H; ATRX (retained), H3 p.K28 (k27M) negative with H3 p. K28me3(K27me) expression retained; BRAF V600E mutation negative



Mostly round cells with a few atypical nuclei



- Molecular: DNA methylation profile aligned with subependymoma



Subependymoma in a 38-year-old male with headaches, nausea, vomiting, and blurred vision. A, B, C. Sagittal, coronal, and axial MRI with a solid, lobulated, heterogeneous lesion in the 3rd ventricle with extension to the frontal horns

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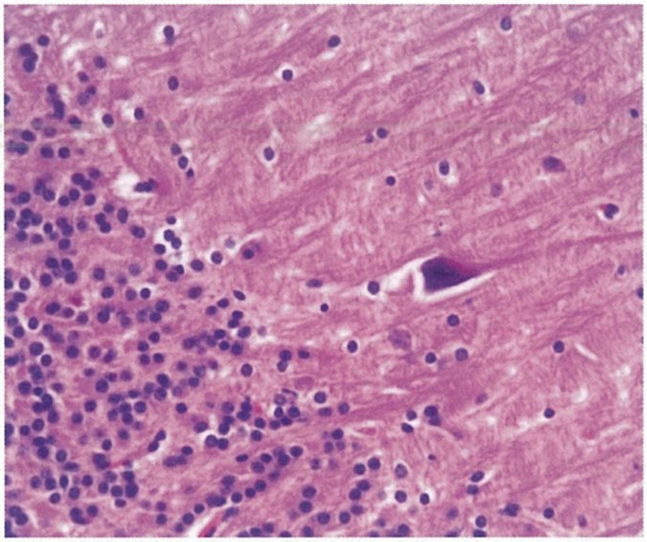


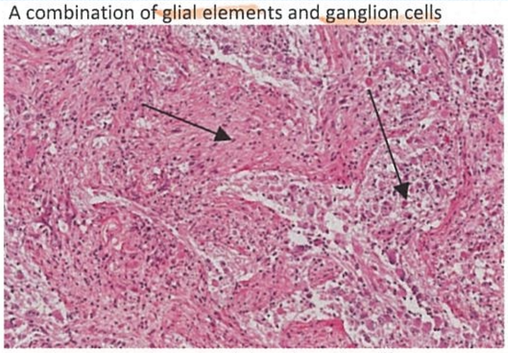
GLIONEURONAL AND NEURONAL TUMORS

SILVIA J. HERNANDEZ, MD

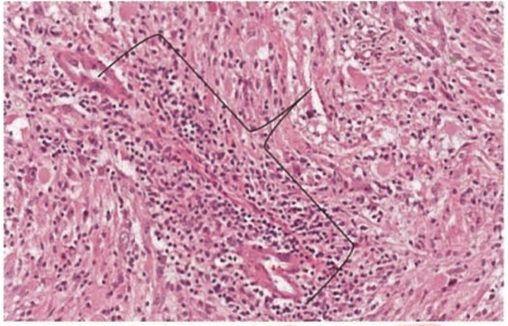
11. GLIONEURONAL AND NEURONAL TUMORS

GLIONEURONAL AND NEURONAL TUMORS

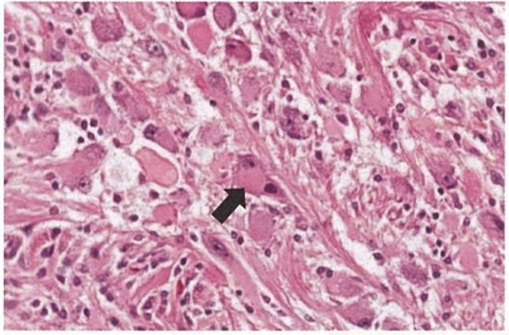
A combination of glial elements and ganglion cells



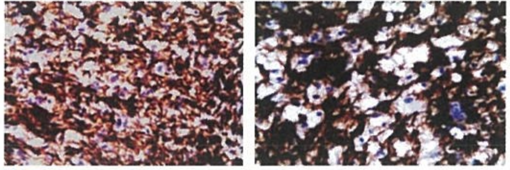
Prominent vasculature with lymphocytic cuffs



Ganglion cells displaying cytomegaly and binucleation

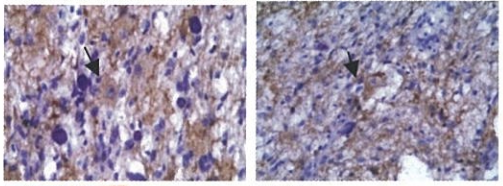


Strong positivity in neoplastic cells of the glial component



GFAP GFAP

Immature neoplastic ganglion cells are highlighted



Synaptophysin CD34

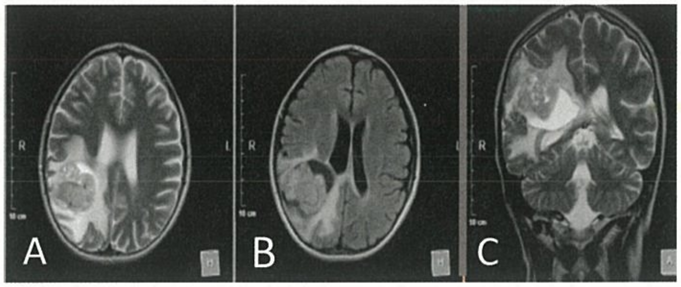
GANGLIOGLIOMA (CNS WHO GRADE 1)

MORPHOLOGY

- Glioneuronal tumor composed of **dysmorphic ganglion cells** admixed with **neoplastic glial elements**
- **Dysmorphic ganglion cell features**: Cytomegaly, perimembranous aggregation of Nissl substance, vesicular nuclei with central nucleoli, **binucleation,** and **clustering "kissing"** cells
- **Glial element features**: Resemble low-grade astrocytomas, hyaline droplets that form eosinophilic granular bodies, Rosenthal fibers with **"oligo-like"** and **"glioma-like"** components
- Other features: Prominent vasculature (especially in the wall of the cystic portion), perivascular lymphocytic cuffs, calcifications and dense fibrous stroma with a reticulin-rich matrix that may form a lobular/nest-like architecture encircling neoplastic cells
- Gross exam: Well-delineated solid or cystic lesion with calcifications

OTHER HIGH YIELD POINTS

- Clinically presents with **focal seizures**; may vary according to size and localization of tumor
- More than 70% occur in the **temporal lobe**
- May be present in other lobes (frontal, parietal, occipital and multiple), as well as the cerebrum, brainstem, cerebellum, spinal cord, optic nerve, and pineal gland
- Most common in the 1^{st}-2^{nd} decade with male predominance
- Imaging:
    - ➢ T1-hypointense, well-demarcated solid or cystic lesion
    - ➢ T2-hyperintense cyst with enhancing nodule
    - ➢ FLAIR with increased signal
- Calcifications may be present in 30% of gangliogliomas
- Calvaria scalloping may be detected in superficial tumors
- Recurrence is uncommon; **excellent prognosis**
- IHC:
    - ➢ Neuronal markers: **(+) synaptophysin, CD34** (ganglion cells), MAP2, chromogranin A, neurofilament; (-) NeuN
    - ➢ **Glial markers**: (+) **GFAP,** OLIG2; (-) IDH1 R132H; Ki-67: 1.1-2.7%
- Molecular: **MAPK pathway activation (BRAF V600E mutation more common in 20-60%)**



Ganglioglioma. 15-year-old-male with headaches, nausea, diplopia, and decreased strength on right upper extremity. A. Axial T2-weighted MRI shows a right parietal solid-cystic cortical/subcortical lesion with edema B. FLAIR MRI shows marked peritumoral brain edema C. Intra-axial right parietal solid cystic lesion with edema on coronal T2-weighted image

Picture courtesy: Victor Romero, MD and Victor Benitez, MD

Path Presenter

ANAPLASTIC GANGLIOGLIOMA (CNS WHO GRADE 3)

MORPHOLOGY

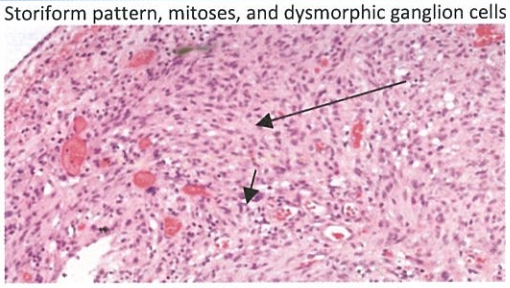
- Subset of ganglioglioma with anaplastic features
- Gross exam: Well-delineated solid or cystic lesion with calcifications
- Dysmorphic ganglion cell features same as grade 1
  Glial element features: **Dense cellularity, mitotic activity, and necrosis**
  Other features: Prominent vasculature, perivascular lymphocytic cuffs, calcifications and dense fibrous stroma made up of a reticulin-collagenous network that forms delicate bridges between blood vessels or a dense, fascicular-storiform pattern

OTHER HIGH YIELD POINTS

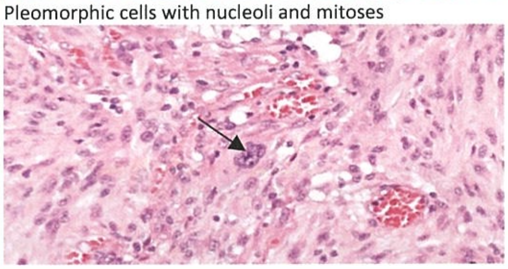
- IHC:
  - Neuronal markers: (+) synaptophysin, nestin (stem cells)
  - Glial markers: (+) GFAP
  - **Ki-67 high**
- Molecular: MAPK pathway activation (BRAF V600E mutation)

Path Presenter

Storiform pattern, mitoses, and dysmorphic ganglion cells



Pleomorphic cells with nucleoli and mitoses



GANGLIOCYTOMA (CNS WHO GRADE 1)

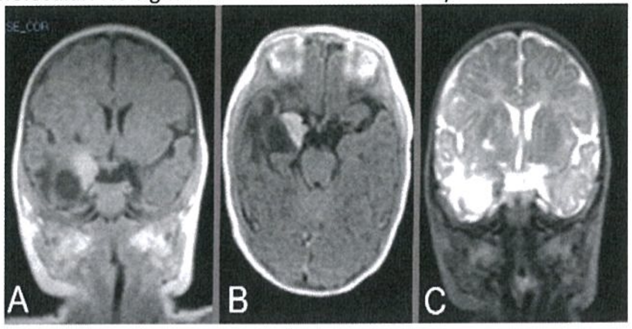
MORPHOLOGY

- Glioneuronal (neuroepithelial) tumor composed of **mature ganglion cells** with **dysplastic features (loss of polarity)**
- **Ganglion cells**: Singles, clustering, binucleated, cytoplasmic ballooning
- Fibrillar or vacuolated matrix (background) that resembles neuropil
- **Other features**: Small neurons, intermediate-size ganglion cells with atypical nuclei and intranuclear cytoplasmic inclusions, basophilic Nissl substance toward the periphery, calcospherites, and perivascular lymphocytes
- Gross exam: Well-delineated solid or cystic lesion that may be gritty

OTHER HIGH YIELD POINTS

Path Presenter

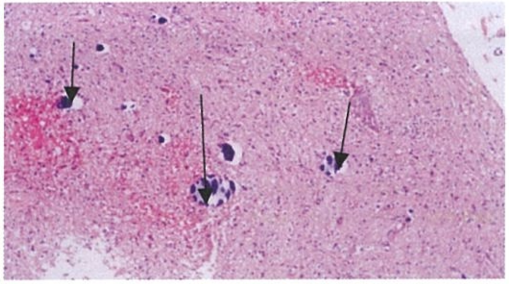
- Clinically presents with focal seizures
- More than 80% occur in the **temporal lobe**
- May be present in other lobes, brainstem, cerebellum, spinal cord, optic nerve, and pineal gland
- Predominantly affects **children**
- Imaging: Well-demarcated solid or cystic lesion; T1-isointense; T2-hyperintense with contrast enhancement after gadolinium administration
- Recurrence is uncommon; **excellent prognosis**
- IHC: **Neuronal markers:** (+) synaptophysin, CD34, MAP2, chromogranin A, neurofilament; glial markers: (+) GFAP in reactive astrocytes; Ki-67 low
- Molecular: No signature molecular abnormality



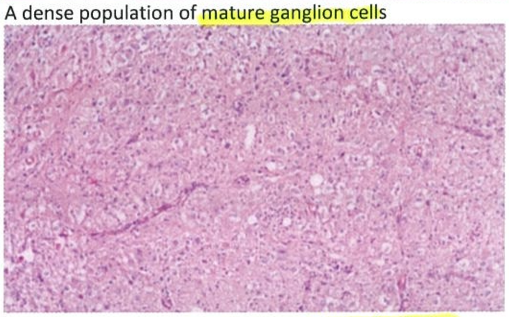
Gangliocytoma in a 2-year-old male with seizures. A. T1-weighted MRI with a solid-cystic lesion near the cortex B. T1-weighted coronal section with hyperintensity in the solid portion of the lesion C.T2-weighted MRI with an isointense, temporal cystic lesion with a solid isointense lesion

Picture courtesy: Victor Romero, MD and Dr. Guillermo Cazares

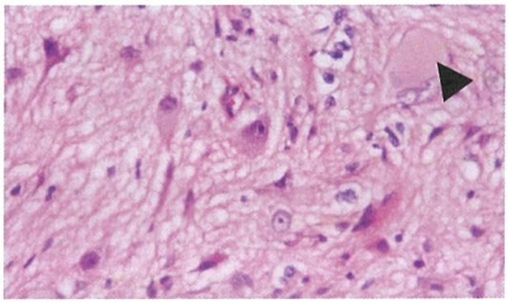
Areas of calcifications, hemorrhage, and lymphocytic cuffs



A dense population of mature ganglion cells



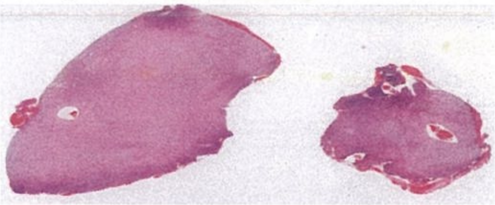
Ganglion cells of different sizes with loss of polarity; binucleated ganglion cell with cytoplasmic ballooning (arrowhead)



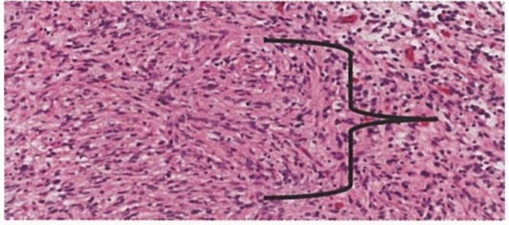
11. GLIONEURONAL AND NEURONAL TUMORS

DESMOPLASTIC INFANTILE GANGLIOGLIOMA (DIG)/DESMOPLASTIC INFANTILE ASTROCYTOMA (DIA) (CNS WHO GRADE 1)

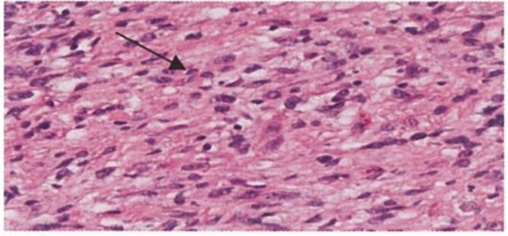
Solid, highly cellular neoplasm with some blood vessels



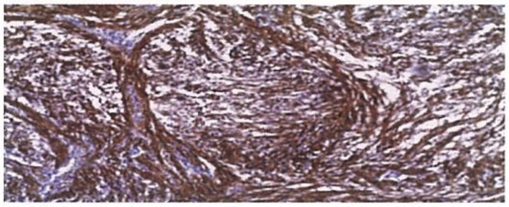
Desmoplastic tissue forming a storiform pattern



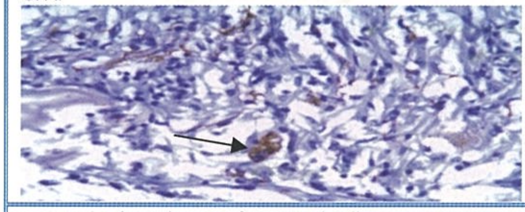
Fibroblast-like spindle cells with no atypia



CD34



GFAP

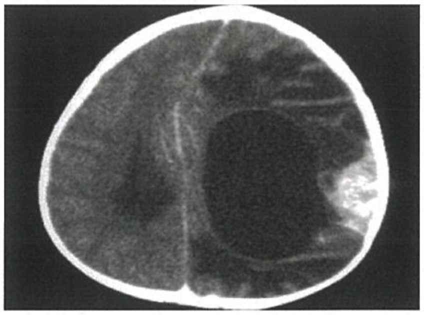


MORPHOLOGY

- Glioneuronal tumors with a desmoplastic, leptomeningeal component
- **DIG**: Mixed neuronal and astrocytic components
- **DIA**: Neoplastic astrocytic component lying in a **desmoplastic stroma**
- Other features: Fibroblast-like spindle cells intermixed with collagen, **reticulin-rich** basal lamina that surrounds individual cells, small foci of primitive **"embryonal-like"** cells, calcifications, and angiomatoid vessels
- Gross exam: Superficial, rubbery or "woody" white-gray lesion attached to the dura that abuts the underlying glial tissue; may have unilocular or multilocular cysts filled with clear or xanthochromic content

OTHER HIGH YIELD POINTS

- Clinically presents with **seizures,** lethargy, **and increased head circumference** with evidence of fontanelle bulging and the **"sunset sign"**
- Cerebral hemispheres with **involvement of the cortex and leptomeninges**; **attachment to the dura**
- Most common in the **first 2 years of life**; M:F ratio of 1.8:1
- Imaging: Large (up to 13 cm) lesion with **2 components — solid (peripheral)** with contrast enhancement after gadolinium and **cystic (deeper)** with hypo- and hyperdensity on T1 and T2 (MRI)
- Recurrence is uncommon with total resection; **excellent prognosis**
- IHC:
  - Neuronal markers: (+) synaptophysin, neurofilament, NeuN
  - Glial markers: (+) GFAP
  - Ki-67 low
- Molecular: **MAPK pathway alterations: BRAF or RAF1 mutation or fusion in the absence of homozygous deletion of CDKN2A and/or CDKN2**



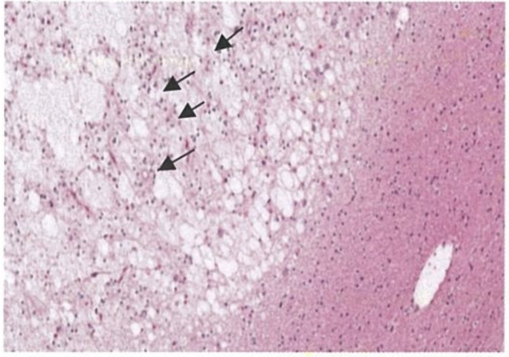
Desmoplastic infantile ganglioglioma. CT scan shows a large cystic mass with peripheral enhancement at the solid portion which is attached to the overlying dura

Picture courtesy: Oluwole Fadare, MD

Path Presenter

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOR (DNT) (CNS WHO GRADE 1)

Perpendicular columns of neuronal cells and axons



Nodular architecture with mucin pools

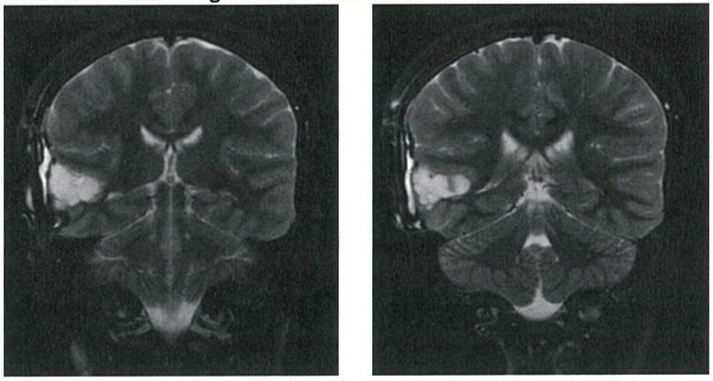
MORPHOLOGY

- Glioneuronal tumor composed of small, round, **"oligodendrocyte-like"** cells and **bundles of axons** arranged in columns
- Oriented perpendicular to the cortical surface
- Other features: **Nodular/lobulated** architecture; non-neoplastic **neurons** "floating" in mucin pools; association with cortical dysplasia
- Gross exam: Superficial, rubbery, white-gray lesion attached to the dura that may have a unilocular or multilocular cyst filled with clear contents

OTHER HIGH YIELD POINTS

- Clinically presents with an **early onset of epilepsy**
- Most common in the **temporal lobes** with involvement of the cerebral cortex
- Common in **children and young adults**; slight predominance in males
- Imaging: Thickness of the normal cortex with a lobulated architecture, sharply defined margins; MRI: T1-weighted images with hypo- or isointense cystic lesions; T2-weighted and FLAIR hyperintense; **"soap bubble"** appearance; rim sign, triangle cortical base, and bone remodeling

- Recurrence is uncommon with total resection; **excellent prognosis**
- IHC:
  - Neuronal markers: (+) NeuN
  - Glial markers in “oligo-like” cells: (+) S100, **OLIG2**, PDGFRA; (-) **GFAP**
- Molecular: **Activating mutations of FGFR1**



Dysembryoplastic neuroepithelial tumor in a 13-year-old-boy with a temporal lesion. MRI T2-weighted coronal sections visualizing hyperintense intracortical nodules with characteristic “bubbly” appearance in the right temporal lobe region and no peritumoral edema

Picture courtesy: Felipe D´Almeida Costa, MD

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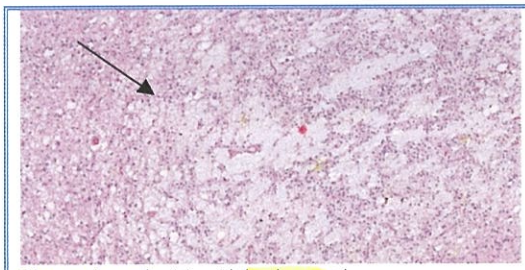
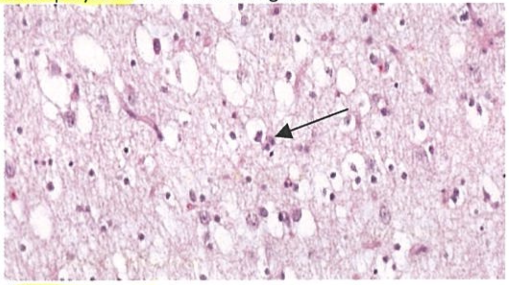
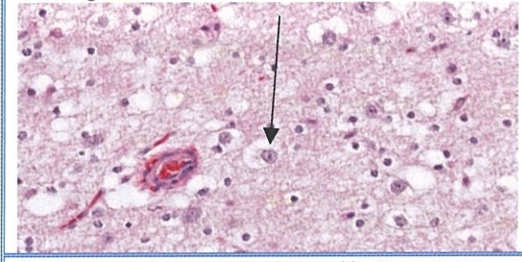


Mucopolysaccharide-rich background



“Floating” neurons



Neurocytes with an oligodendrocyte-like appearance

Picture courtesy: Jared Ahrendsen, MD

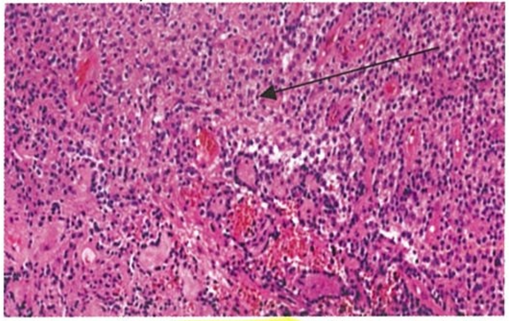
PAPILLARY GLIONEURONAL TUMOR (PGNT) (CNS WHO GRADE 1)

MORPHOLOGY

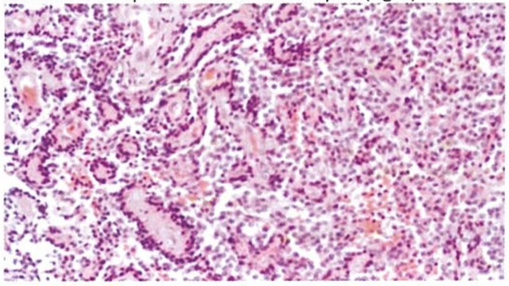
- Glioneuronal (biphasic) tumor composed of neuronal and astrocytic cells
- Neuronal elements: **Neurocytes** of variable shapes and sizes with accompanying neuropil that may resemble **“oligodendrocyte-like”** cells
- Glial elements: **Pseudopapillary structures** formed by hyalinized blood vessels which are covered by flat/cuboidal cells with round nuclei and scant cytoplasm in a single or pseudostratified layer
- Other features: Fibrillary or microcystic background, ganglion cells, mini gemistocytes, eosinophilic granular bodies, microcalcifications, and hemosiderin pigment at the periphery; very rare mitoses
- Gross exam: Solid portion gray and friable with calcifications

OTHER HIGH YIELD POINTS

- Clinically presents with **seizures, headaches**, and neurologic disturbances
- More common in **temporal** and **frontal lobes** and in close **proximity to the ventricles**; may have an intraventricular growth (4th ventricle)
- Predominantly affects **young adults** without male or female predominance
- Imaging including four major presentations:
  - Cystic with a mural nodule
  - Cystic only
  - Solid-cystic masses
  - Solid only
- Recurrence is uncommon; **excellent prognosis**
- IHC:
  - Neuronal markers: (+) synaptophysin, NeuN, neuron-specific enolase (in neurons and neuropil)
  - (+) CD34 and neurofilament (focally) in ganglion cells
  - Glial markers: (+) GFAP, S100 in cuboidal glial cells
  - **(+) OLIG2 in oligodendrocyte-like cells**



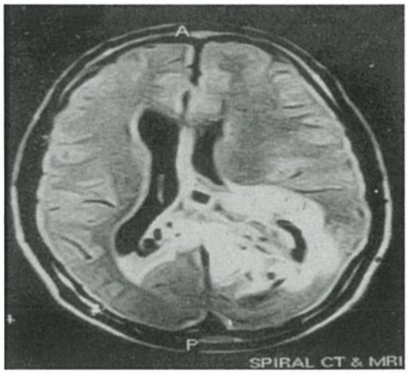
Areas of small papillary structures (left) intermixed with a solid area composed of small neurocytes (right)

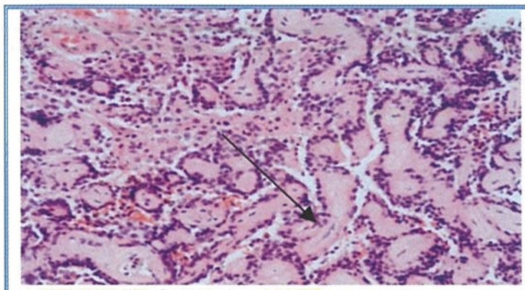


Pseudopapillary structures formed by hyalinized vessels

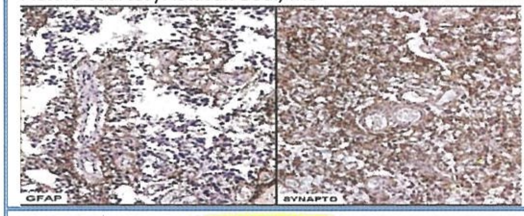
- Molecular: **PRKCA gene fusion (mainly SLC44A1: PRKCA fusion)**

Papillary glioneuronal tumor. Non-contrast MRI brain showing hyperintense lesion involving the left temporal and parieto-occipital regions. The tumor is crossing the midline to the right parietal region
Picture courtesy: Radotra BD, Kumar Y, Bhatia A, Mohindra S

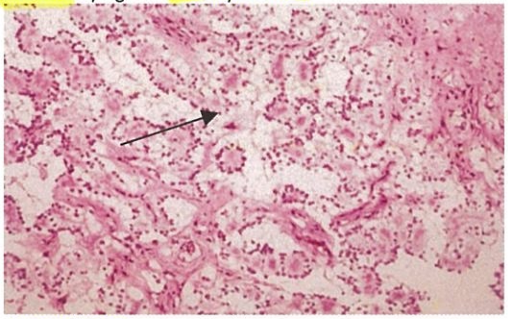




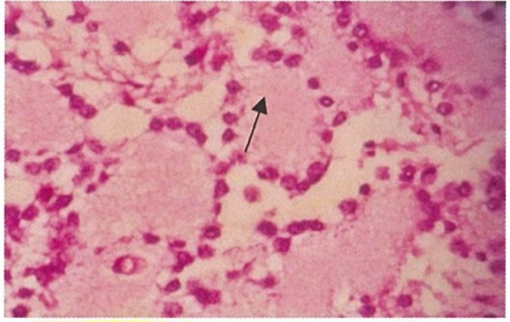
Pseudopapillae formed by GFAP-positive cells; synaptophysin-positive cells forming solid areas
Picture courtesy: Istavan Bodi, MD



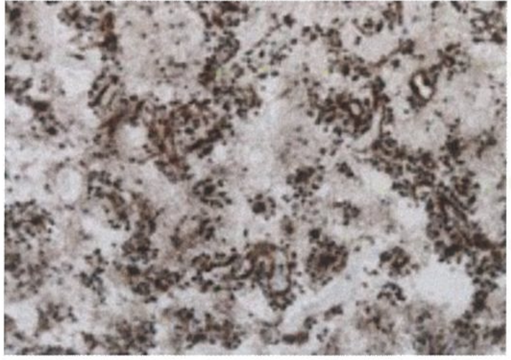
Rosettes lying in a microcystic matrix



Neuropil cores surrounded by neurocytic nuclei
Picture courtesy: Felipe D´Almeida Costa, MD



Synaptophysin-positive neuronal cells
Picture courtesy: Jensflorian, MD



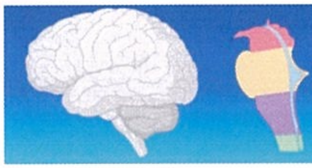
ROSETTE-FORMING GLIONEURONAL TUMOR (RGNT) (CNS WHO GRADE 1)

MORPHOLOGY

- Glioneuronal mixed tumor composed of neuronal and astrocytic cells
- Neuronal elements:
  - Neurocytes with spherical nuclei, finely granular chromatin, and delicate cytoplasmic processes that form rosettes and/or perivascular pseudorosettes
  - Form **ring-shaped arrays of neurocytic nuclei around a delicate, eosinophilic neuropil core** that lie in a microcystic or mucinous matrix resembling pilocytic astrocytoma
- Glial elements: Astrocytic spindle-stellate cells forming a compact/loosely fibrillary or microcystic background
- Other features:
  - **"Oligodendrocyte-like"** cells, Rosenthal fibers, eosinophilic granular bodies, microcalcifications, hemosiderin, ganglion cells (occasional)
  - Thin-walled, dilated, hyalinized, sometimes thrombosed or glomeruloid-appearing vessels
- Gross exam: Well-demarcated, soft, gelatinous tumors

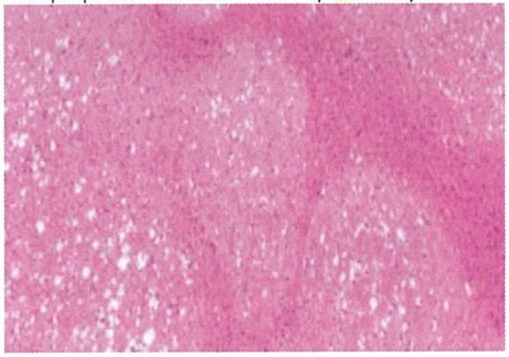
OTHER HIGH YIELD POINTS

- Clinically presents with **headaches and ataxia,** papilledema, vertigo, dysarthria, blurred vision, and diplopia
- Common in the midline around the **4th ventricle** and aqueduct and may extend to adjacent brainstem; also seen in cerebellar vermis, pineal gland, and thalamus
- Most common in young adults, adolescents and children
- Imaging: Solid, solid-cystic, or multicystic tumors
- Recurrence is uncommon with total resection; **excellent prognosis**
- IHC:
  - Neuronal markers: (+) synaptophysin, MAP2, NeuN, OLIG2
  - Glial markers: (+) GFAP, S100
- Molecular: **FGFR1 mutation with co-occurrence of PIK3CA and/or NF1 mutation**

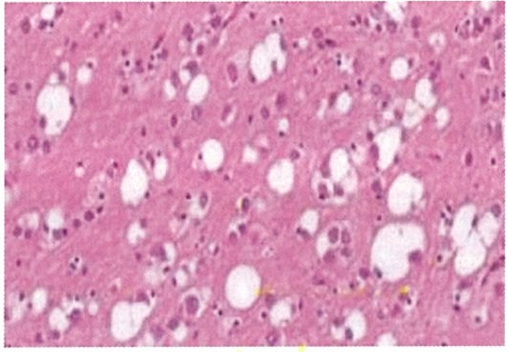


11. GLIONEURONAL AND NEURONAL TUMORS

Multiple pale nodules surrounded by a fibrillary matrix



Delicate vacuolar changes
Picture courtesy: Jared Ahrendsen, MD



MULTINODULAR AND VACUOLATED NEURONAL TUMOR (MVNT) (CNS WHO GRADE 1)

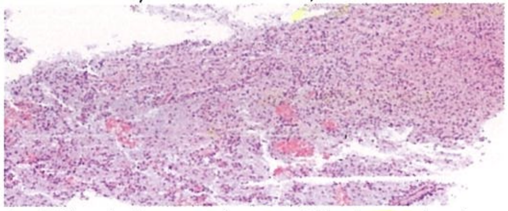
MORPHOLOGY

- Glioneuronal tumor composed of neuronal elements that lie in a delicate fibrillary matrix formed by discrete, coalescent nodules with vacuolar changes
- Neuronal elements: Neuronal cells of intermediate to large size with round vesicular nuclei, distinct nucleoli, and eosinophilic-amphophilic cytoplasm with cytoplasmic or pericellular vacuolization; distributed haphazardly within nodules or along capillary vessels
- Glial elements: Delicate fibrillary matrix that forms **pale, hypomyelinated nodules** with conspicuous **vacuolar changes**
- Other features: **"Oligodendrocyte-like"** cells intermingled or clustered; may be associated with regional cortical disorganization or hippocampal sclerosis
- Gross exam: Multiple, discrete, coalescent gray nodules that involve the deep cortex, gray-white junction, and subcortical white matter

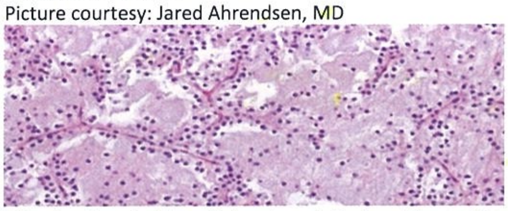
OTHER HIGH YIELD POINTS

- Clinically presents with **seizures**, headaches, episodic confusion, and dizziness
- **Temporal lobes; usually in adults, rarely in children**
- Imaging: Thickness of the normal cortex, lobulated architecture, sharply defined margin, absence of mass effect, and no significant peritumoral edema
- Recurrence is uncommon with total resection; **excellent prognosis**
- IHC: Neuronal markers: (+) **OLIG2**, HuC/HuD, non-phosphorylated 200-kDa NFP, internexin A, **synaptophysin**, MAP2, CD34; (-) NeuN, chromogranin
- Molecular: **MAPK pathway-activating abnormalities**, mutations in MAP2K1, BRAF and FGFR2 fusions

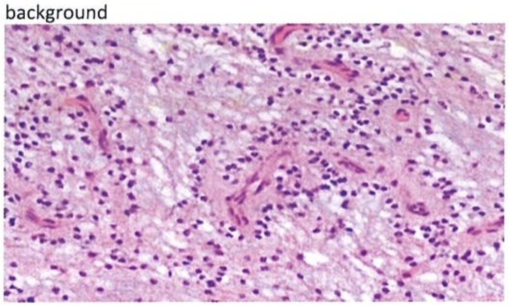
Neoplastic cells and prominent mucoid-like areas
Picture courtesy: Chandra Krishnan, MD



Small "floating" neurons in a myxoid background and a delicate vasculature
Picture courtesy: Jared Ahrendsen, MD



Oligodendrocyte-like cells in a loosely textured basophilic background



MYXOID GLIONEURONAL TUMOR (MGNT) (CNS WHO GRADE 1)

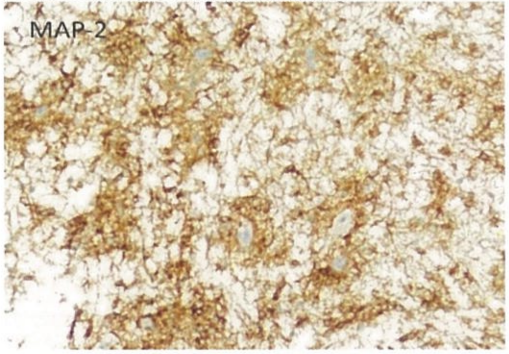
MORPHOLOGY

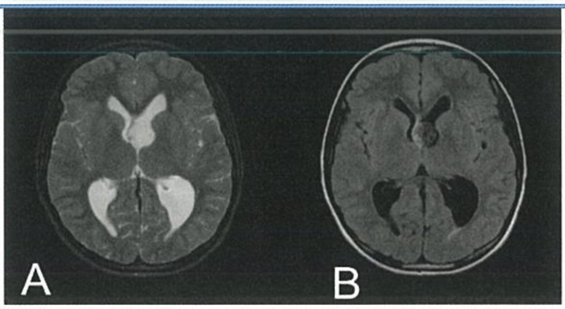
- Glioneuronal tumor composed of **"oligodendrocyte-like"** cells in a prominent myxoid background
- Neuronal elements resemble DNT ("floating" neurons) or could resemble rosette-forming glioneuronal tumor (neurocytic rosettes)
- Gross exam: Soft, gelatinous, gray lesions

OTHER HIGH YIELD POINTS

- Clinically presents with headaches, emesis, seizures, and behavioral disturbances
- Most common in septum nuclei and septum pellucidum; less frequently in the corpus callosum, genu, and periventricular white matter of lateral ventricles
- Confirmed cases in adults (median age 42) and few in children
- Imaging: T1-hypointense and T2-hyperintense, well-circumscribed lesions without contrast enhancement or restricted diffusion
- Favorable outcome
- IHC:
  - Neuronal markers: (+) OLIG2, SOX10, GFAP, and MAP2 in oligodendrocyte-like cells
  - Synaptophysin is positive in floating neurons, neurocytic rosettes, and perivascular neuropil
- Molecular: **PDGFRAp.K385L/I dinucleotide mutation or PDGFRA mutations (extracellular domain)**

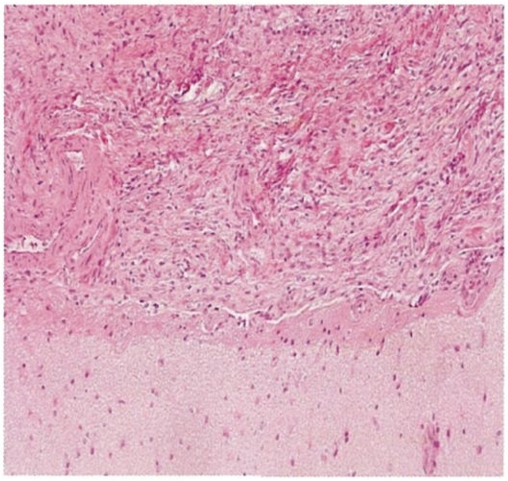
MAP2 positivity in neuronal cells
Picture courtesy: Chandra Krishnan, MD

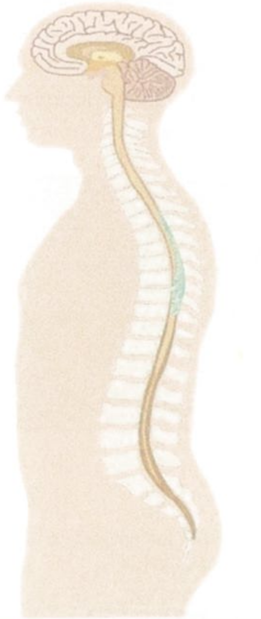




Myxoid glioneuronal tumor in a 5-year-old (photomicrographs in left column correspond with this case). A. T2-weighted MRI shows a predominantly hyperintense, well-defined, round lesion on the left lateral ventricle
B. Round hypointense lesion on FLAIR
Picture courtesy: Chandra Krishnan, MD

Monomorphic neoplastic cells that infiltrate the leptomeninges in a diffuse manner and form a storiform pattern
Picture courtesy: Sonika Dahiya, MD





Sagittal section: Diffuse leptomeningeal tumor in leptomeningeal space

DIFFUSE LEPTOMENINGEAL GLIONEURONAL TUMOUR (DLGNT) (CNS WHO GRADE 2 & 3)

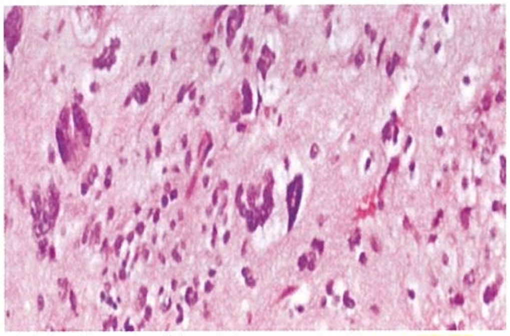
MORPHOLOGY

- Glioneuronal tumor affecting the leptomeninges with "**oligodendrocyte-like" cells** that infiltrate the leptomeninges in a diffuse manner or in small nests with desmoplastic areas (may have a storiform pattern or myxoid changes)
- Other features: Ganglion cells, neuropil and neuropil-like islands, neurocytic rosettes, eosinophilic granular bodies
- Gross exam: Diffuse leptomeningeal tumor spread with a mucoid appearance on the surface of the parenchyma, intraventricularly, or in leptomeningeal or Virchow spaces

OTHER HIGH YIELD POINTS

- Clinically presents with symptoms of increased intracranial pressure, headache, nausea, and vomiting
- More commonly occurring in cerebral hemispheres within the temporal and frontal lobes and in close proximity to the ventricles; may have intraventricular growth
- Predominantly **affects children**; male predominance
- Imaging:
  - Diffuse thickening along the spinal cord which may extend to the posterior fossa, brainstem, and basal cisterns
  - Small, cystic or nodular, T2-hyperintense lesions along the subpial surface of the spinal cord or brain
  - Intraparenchymal lesions, most commonly seen in the spinal cord
- **CNS WHO grade 2** (conventional and DLGNT-MC-1 profile) and **grade 3** (with anaplastic features, 1q gain, and/or DLGNT-MC2 profile)
- DLGNT-MC-1 (better prognosis); DLGNT-MC-2 (worse prognosis)
- IHC:
  - Neuronal markers: (+) OLIG2, MAP2, and S100 (**"oligodendrocyte-like"** cells)
  - (+) synaptophysin (neuropil aggregates); (-) NeuN, neurofilament
  - (+) GFAP (less than 50% of neoplastic cells)
- Molecular: **MAPK pathway alteration (most commonly KIAA1549:BRAF fusion) and 1p deletion**

11. GLIONEURONAL AND NEURONAL TUMORS



Multinucleated cell (nuclei arranged as "pennies on a plate") Picture courtesy: Jared Ahrendsen, MD

DIFFUSE GLIONEURONAL TUMOR WITH OLIGODENDROGLIOMA-LIKE FEATURES AND NUCLEAR CLUSTERS (DGONC) (CNS WHO GRADE 1)

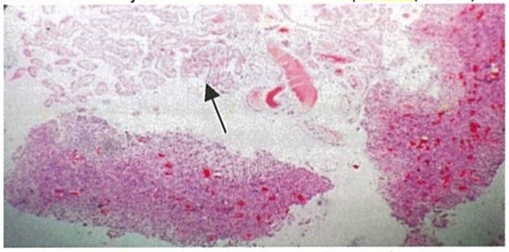
MORPHOLOGY

- Glioneuronal tumor composed of small to medium **"oligodendrocyte-like"** cells and scattered **multinucleated** cells with nuclei arranged on the periphery like "pennies on a plate" or in **clusters**

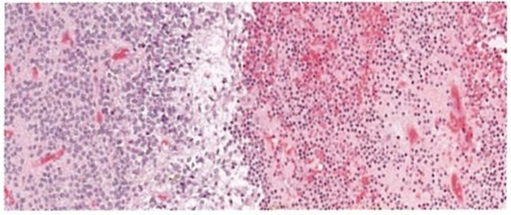
OTHER HIGH YIELD POINTS

- Most common in supratentorial regions: **Temporal**, parieto-occipital, and frontal lobes as well as lateral ventricles
- Most common in **children** but also reported in adults; no sex predilection
- Prognosis: 5-year overall survival rate reported as 89%
- IHC: (+/-) synaptophysin on **neuropil background; (+) OLIG2; (-) GFAP**
- Molecular: Distinct methylation profile and frequent **monosomy 14**

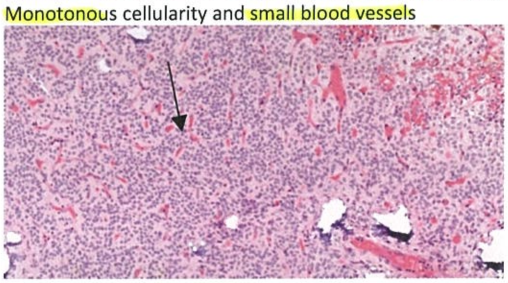
Tumor cells adjacent to normal choroid plexus (arrow)



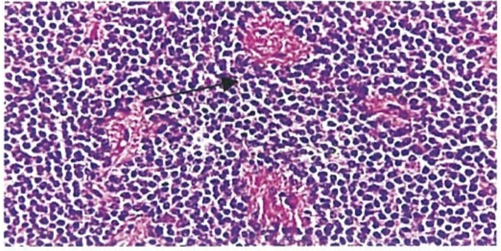
Perinuclear halos, blood vessels and hemorrhagic areas



Monotonous cellularity and small blood vessels



Small cells surrounded by neuropil



Fibrillary (neuropil-like) areas surrounded by small nuclei with salt and pepper chromatin

Path Presenter

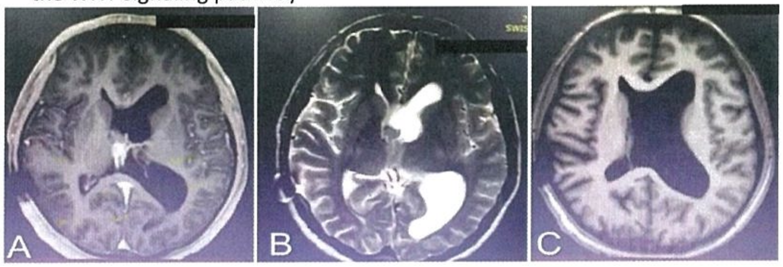
CENTRAL NEUROCYTOMA (CN) (CNS WHO GRADE 2)

MORPHOLOGY

- Neuroepithelial tumor composed of small, isomorphous, **uniform, round neuronal cells** with a round to oval nucleus, finely **speckled chromatin**, and an inconspicuous nucleolus lying in fibrillary areas mimicking neuropil
- Architectural patterns: Oligodendroglioma-like honeycomb architecture, large fibrillary areas mimicking the irregular rosettes in pineocytomas, cells arranged in straight lines and perivascular pseudorosettes, capillary blood vessels in an arborizing pattern, calcifications, Homer Wright rosettes, and ganglioid cells
- Gross exam: Grayish, friable tumor with calcifications

OTHER HIGH YIELD POINTS

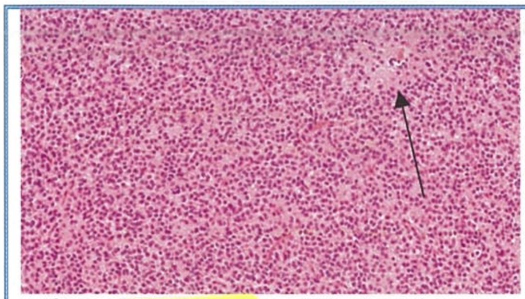
- Clinically presents with symptoms of **increased intracranial pressure** (headache, nausea, and vomiting)
- The most common location is the anterior portion of the **lateral ventricles**, usually attached to the **septum pellucidum** near the foramen of Monro
- Most common between **20-40 years** of age without male or female predominance
- Imaging: MRI T1-isointense with a soap-bubble multicystic appearance on T2-weighted images; calcifications and hemorrhage may be seen
- **Good prognosis** in cases with total resection
- IHC: Neuronal markers: (+) synaptophysin (most reliable marker in the tumor matrix), NeuN, TTF1 (clone SPT24), MAP2, L1CAM (ganglion cells); (+/-) OLIG2
- Molecular: No diagnostic molecular features; occasional findings include numerous DNA copy number alterations, MYCN gain, and overexpression of the WNT signaling pathway



Picture courtesy: Silvia Alvarez, MD

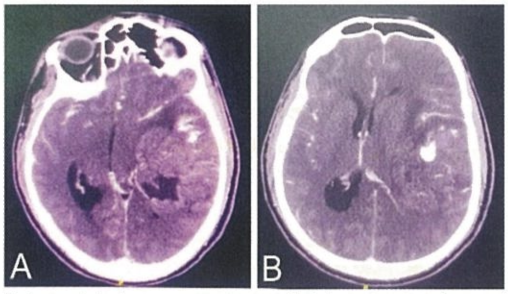
Central neurocytoma in a 20-year-old male with headaches, vomiting, and bilateral visual loss. A. Axial T1-weighted MRI with a hypointense lesion in the right ventricle
B. T2-weighted nodular isointense lesion
C. T1-weighted MRI showing a hyperintense lesion with moderate hydrocephalus

11. GLIONEURONAL AND NEURONAL TUMORS



Uniform, round neurocytes, small blood vessels, and discrete areas of neuropil

Picture courtesy: Jared Ahrendsen, MD



Extraventricular neurocytoma. Axial contrast-enhanced CT scan showing a poorly defined intraparenchymal left temporal lesion with compression of the ipsilateral ventricle and subsequent ventricle displacement, midline displacement to the right, and decrease in adjacent subarachnoid space

Image courtesy: Komala Gangaiah, MD

EXTRAVENTRICULAR NEUROCYTOMA (EVNC) (CNS WHO GRADE 2)

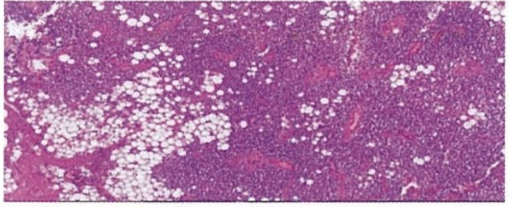
MORPHOLOGY

- Neuronal-glial tumor composed of **uniform, round neuronal cells** lying in fibrillary areas mimicking neuropil
- Architectural patterns: **Wide morphologic spectrum** with oligodendroglioma-like cells with perinuclear halos, monotonous neurocytes in sheets, clusters, ribbons, and sometimes ganglion or gangliod cells; hyalinized vessels and calcifications may be present
- Gross exam: Grayish, friable tumor with calcifications

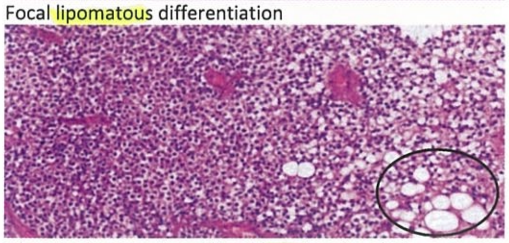
OTHER HIGH YIELD POINTS

- Clinically presents with symptoms related to location and may include headaches, seizures, visual disturbances, hemiparesis, cognitive disturbances, or epilepsy
- May also involve motor, sensory, or sphincter dysfunction
- The most common locations are the **cerebral hemispheres** (involving the cortex and subcortical white matter) and cerebellum
- Most common between 3rd and 4th decades without male or female predominance
- Imaging: Large, well-demarcated, solid-cystic lesion with peritumoral edema, solid portion is isointense to hypointense on T1-weighted MRI and hyperintense on T2-weighted images
- **Good prognosis** in cases with total resection
- IHC:
  - Neuronal markers: (+) **synaptophysin (tumor cells and neuropil islands)**, NeuN, chromogranin, GFAP (50% of the cases); (+/-) OLIG2
  - Ki-67 loss (1-3%)
- Molecular: **FGFR1:TACC1 fusion** and other FGFR alterations

Lipid-laden cells combined with small neuronal cells

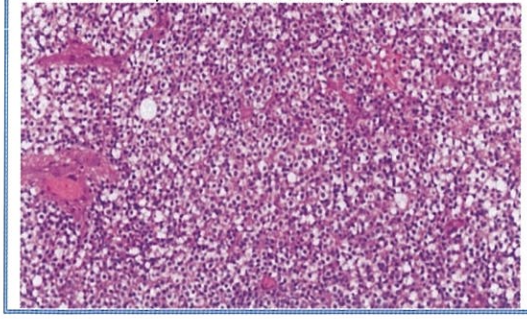


Focal lipomatous differentiation



Oligodendrocyte-like cells with perinuclear halos

Picture courtesy: Daniel Kassie Molla, MD



CEREBELLAR LIPONEUROCYTOMA (CNS WHO GRADE 2)

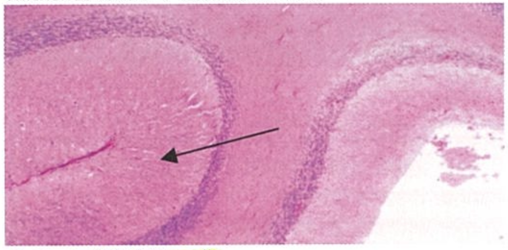
MORPHOLOGY

- Neuroepithelial tumor composed of small, isomorphous, **uniform, round neuronal cells** with round to oval nuclei, clear cytoplasm, and poorly defined cell membranes arranged in sheets and lobules combined with focal **accumulation of lipid-laden cells** (lipomatous differentiation of neuroepithelial tumor cells)
- Oligodendroglioma-like honeycomb architecture, large fibrillary areas mimicking the irregular rosettes in pineocytomas, cells arranged in straight lines and perivascular pseudorosettes, capillary blood vessels in an arborizing pattern, calcifications, Homer Wright rosettes, and ganglioid cells
- Gross exam: Non-specific characteristics

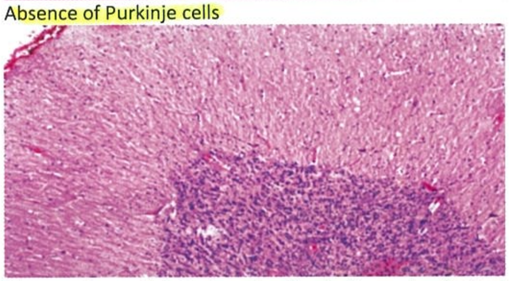
OTHER HIGH YIELD POINTS

- Clinically presents with symptoms of increased intracranial pressure
- The most common location is the anterior portion of the **lateral ventricles, usually attached to the septum pellucidum** near the foramen of Monro
- Most common between 20 and 40 years with no male or female predominance
- Imaging: MRI T1-isointense with **patchy areas of hyperintensity due to lipid content on T2-weighted images**
- **Favorable prognosis** in cases with total resection
- IHC:
  - Neuronal markers: (+) synaptophysin, NeuN, MAP2, GFAP (focal), NSE
- Molecular: **Chromosomes 14 and 2p have shown focal losses**

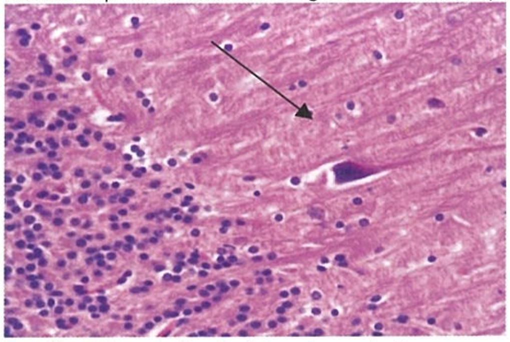
Thickened folia in a transitional zone



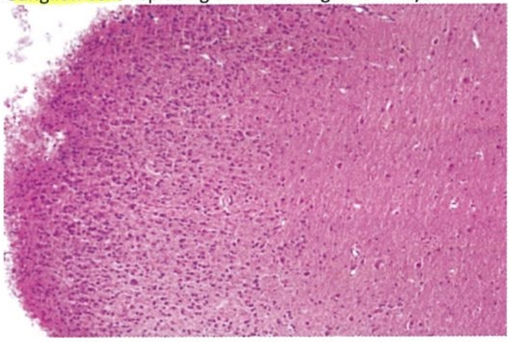
Absence of Purkinje cells



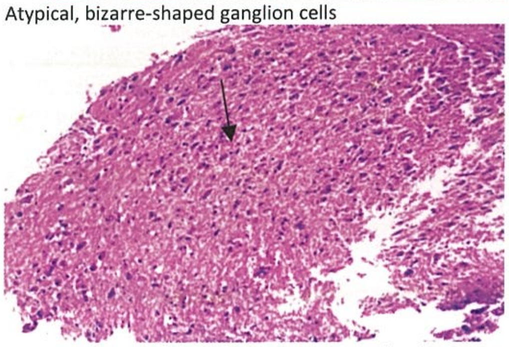
Neurons in parallel stacks extending to the molecular layer



Ganglion cells replacing the internal granular layer



Atypical, bizarre-shaped ganglion cells



Images courtesy: Yolanda Martinez, MD and Leslie Reyes, MD

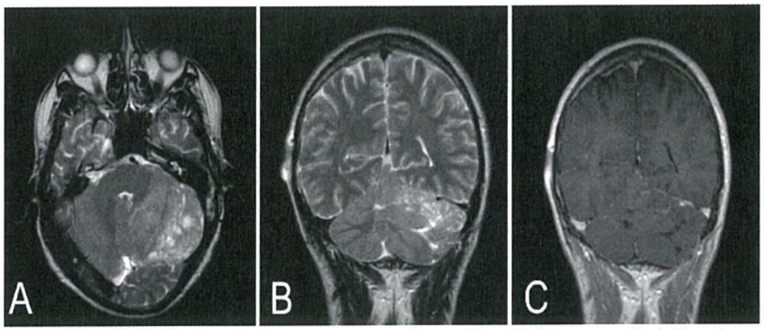
DYSPLASTIC CEREBELLAR GANGLIOCYTOMA (LHERMITTE-DUCLOS DISEASE) (CNS WHO GRADE 1)

MORPHOLOGY

- Neuronal tumor composed of enlarged, **dysplastic ganglion cells** that are located within and **replace the internal granular** layer of the cerebellum, **thickening the** cerebellar folia and conforming to the existing cortical architecture
- Ganglion cells: Singles, clustering, binucleated, cytoplasmic ballooning
- Matrix that resembles a neuropil or a fibrillar or vacuolated background
- Other features: Reduced number of Purkinje cells, large and bizarre neurons, dense capillary network, vacuolization of cerebellar white matter, microcalcifications, abnormal myelination of the molecular layer, abnormal neurons extending from the granular layer in parallel stacks into the molecular zone
- Gross exam: **Enlarged folia** with a yellow-white surface

OTHER HIGH YIELD POINTS

- Clinically presents with ataxia, seizures, hydrocephalus
- May be associated with **Cowden syndrome**, an autosomal dominant disorder with a germline mutation in PTEN that involves the 3 germ cell layers and causes increased risk of breast, thyroid, endometrial, renal, and colon cancers
- Occurs in the cerebellum and may affect both vermis and hemispheres
- Predominantly affects adults in the 3rd or 4th decade
- **Adult-onset is considered pathognomonic for Cowden syndrome**
- Imaging: Non-enhancing, unilateral hemispheric expansion of the cerebellum; MRI T1-weighted hypointense, T2-weighted hyperintense and both with **parallel linear striations (tiger stripes)** or **"corduroy/laminated"** appearance on the surface of the lesion (thickened cerebellar folia)
- **Good prognosis with surgical resection**; some cases with local recurrence; prognosis in general is associated with other neoplasms of Cowden syndrome
- IHC:
  - Neuronal markers: (+) MAP2, chromogranin A, neurofilament, synaptophysin
  - Glial markers: (+) GFAP in reactive astrocytes
- Molecular: No signature molecular abnormality



30-year-old male with headaches, nausea, and vomiting (microscopy in left column corresponds with this case).

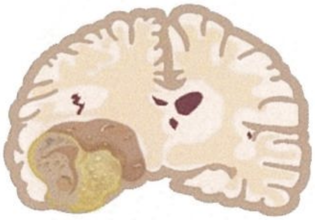
A. T2-weighted MRI showing mass effect caused by unilateral expansion and thickening of the cerebellum folia with hyperintense, parallel linear striations B. T2-weighted coronal section showing the thickening and enlargement of the cerebellar folia causing edema on the left cerebellar hemisphere

C. T1-weighted, contrast-enhanced coronal section showing a hypointense distortion of the cerebellar folia

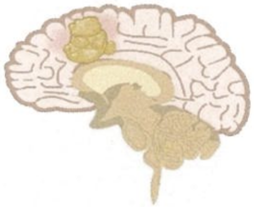
Image courtesy: Silvia Alvarez, MD and Pedro Hernandez, MD

11. GLIONEURONAL AND NEURONAL TUMORS

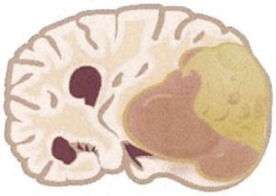
GLIONEURONAL AND NEURONAL TUMORS: GROSS ILLUSTRATIONS



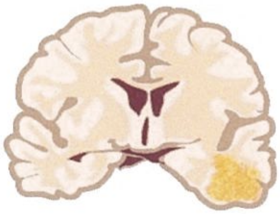
GANGLIOGLIOMA: Coronal section showing well-delineated solid or cystic lesion with calcifications in the right temporal lobe



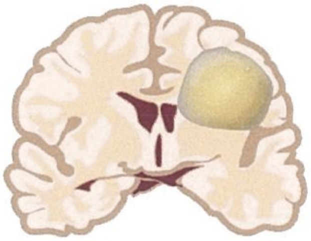
GANGLIOCYTOMA: Mid-sagittal section showing a well-delineated, solid-cystic lesion with a gritty consistency in the left frontoparietal lobes



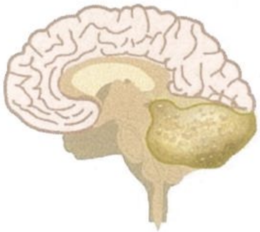
DIA/DIG: Coronal section showing superficial, rubbery or "woody", white-gray lesion attached to the dura that abuts the underlying glial tissue with multilocular cysts filled with clear or xanthochromic contents in the right temporal lobe



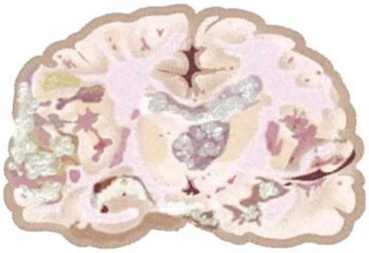
DNT: Coronal section showing superficial, rubbery, white-gray lesion with multilocular cyst filled with clear contents in the right temporal lobe



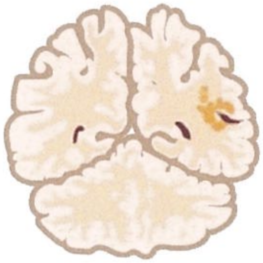
PGNT: Coronal section showing solid, gray, friable lesion with calcifications in the right frontal lobe



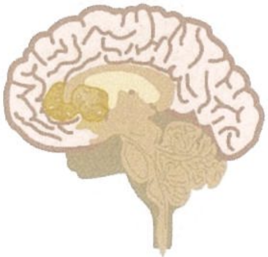
RGNT: Mid-sagittal section showing well-demarcated, soft, gelatinous tumors in the 4th ventricle



DLGNT: Coronal section showing diffuse leptomeningeal tumor spread with a mucoid appearance on the surface of the parenchyma, intraventricularly, or in leptomeningeal or Virchow spaces

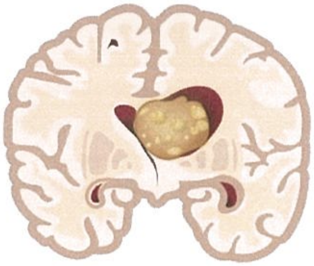
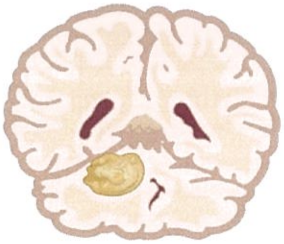
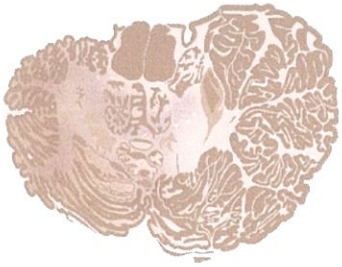


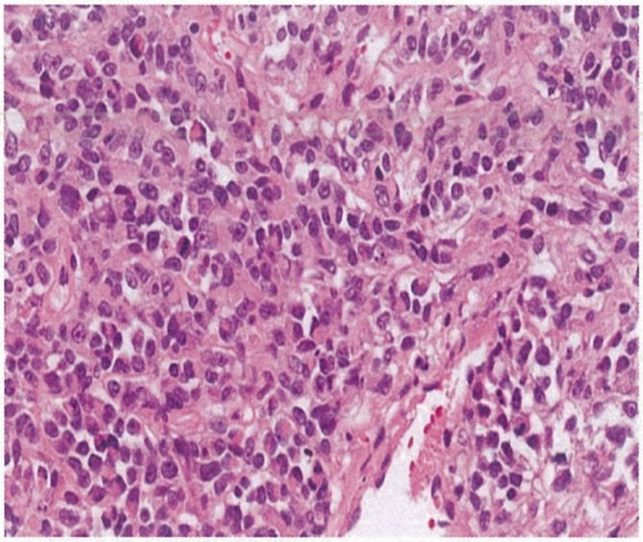
MVNT: Axial section showing multiple discrete, coalescent, gray nodules that involve the deep cortex, gray-white junction, and subcortical white matter in the right temporal lobe



MGNT: Mid-sagittal section showing solid lesion in the septum pellucidum

11. GLIONEURONAL AND NEURONAL TUMORS

		
CENTRAL NEUROCYTOMA: Coronal section showing Intraventricular grayish, friable tumor with calcifications	**CEREBELLAR LIPONEUROCYTOMA:** Axial section showing solid, white-yellow lesion in the cerebellum	**CEREBELLAR DYSPLASTIC GANGLIOCYTOMA:** Coronal section showing **enlarged folia** with a yellow-white surface in the cerebellum

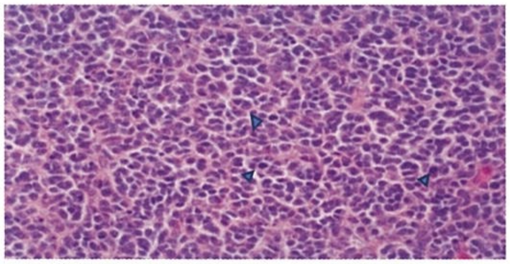


EMBRYONAL TUMORS

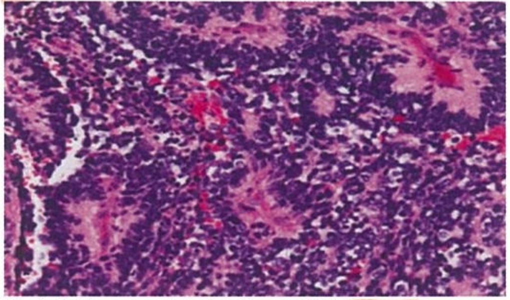
PURVI PATEL, MD, PhD
GABRIELLE YEANEY, MD

12. EMBRYONAL TUMORS

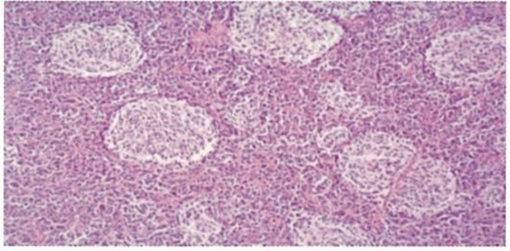
EMBRYONAL TUMORS



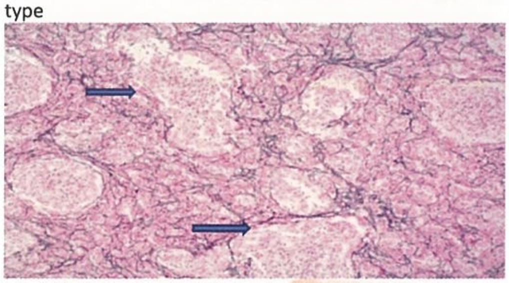
Medulloblastoma. SHH-activated, p53-wildtype, histologically classic type with mitotically active small round blue cells (blue arrowheads)



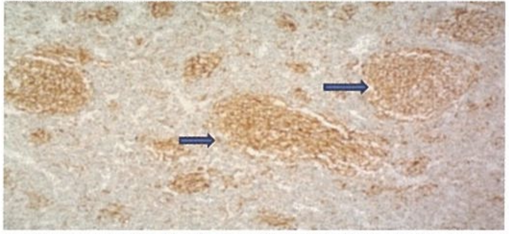
Medulloblastoma showing **Homer Wright rosettes**



Medulloblastoma. Histologically desmoplastic nodular type



Medulloblastoma. Histologically desmoplastic nodular type, reticulin stain highlights reticulin-free zones (pale islands) (blue arrows)



Nodules of desmoplastic/nodular (D/N) histologic subtype are positive for synaptophysin

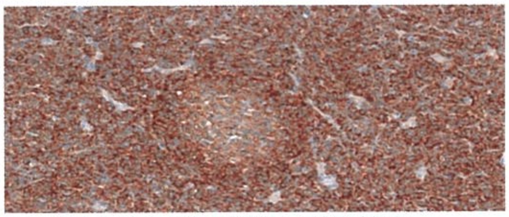
MEDULLOBLASTOMA

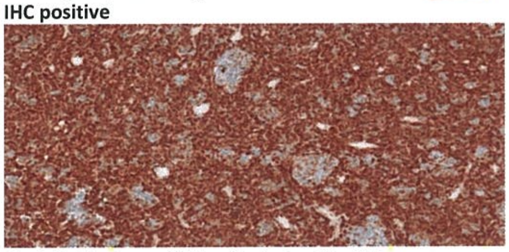
MORPHOLOGY

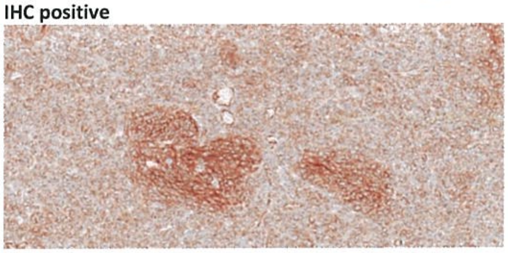
- Grossly, fleshy tumor with hemorrhage and sometimes necrosis
- Microscopically, embryonal neuroepithelial tumor with **small round blue cells** and high N:C ratio
- High mitoses and apoptosis are common with mild to moderate cellular pleomorphism
- Variable **Homer Wright rosettes**
- Different morphologic subtypes show distinct histopathologic features including nodule formation, streaming of cells, and differentiation along lineages including but not limited to neurocytic, ganglionic, myogenic, and melanocytic
- Classified into morphologic types as well as molecular groups and subgroups based on their biologic heterogeneity
- Histologic subtypes:
  - ➢ **Classic type:** Densely packed, poorly differentiated, hyperchromatic, mitotically active, small round blue cells; may have focal nodularity
  - ➢ **Desmoplastic/nodular type (D/N)**: Several nodular, reticulin-free zones (pale islands) with intervening, densely packed, hyperchromatic, poorly differentiated cells with extensive intercellular network of reticulin fibers, predominantly seen in SHH-activated pathway, TP53-wildtype; good prognosis
  - ➢ **Medulloblastoma with extensive nodularity (MBEN):** Large, reticulin-free zones of neurocytic cells against a neuropil-like matrix with expanded lobular/nodular architecture and narrow internodular strands in some areas; Ki-67 proliferation index is high in internodular areas; best prognosis
  - ➢ **Anaplastic/large cell type (LC/A):** Large, monomorphic cells with prominent nucleoli and anaplastic cells with marked nuclear pleomorphism, numerous mitoses, and apoptosis; frequent nuclear molding, cell wrapping, and cytoplasmic pseudoinclusions; predominantly seen in non-WNT/non-SHH group 3 or SHH-activated, TP53-mutant molecular subgroups; high risk, worst prognosis

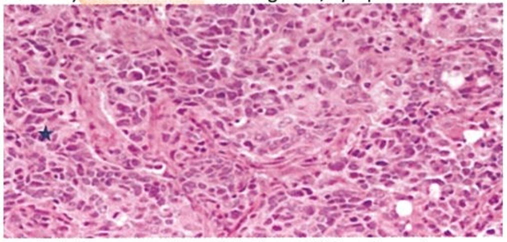
OTHER HIGH YIELD POINTS

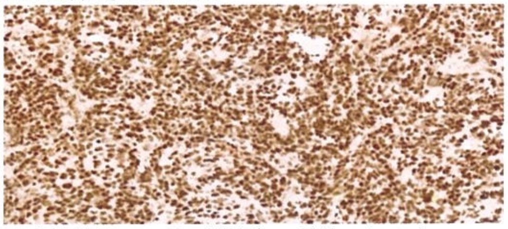
- **CNS WHO grade 4 tumor**, 2nd most common CNS malignant tumor in children
- Accounts for approximately 20% of intracranial neoplasms in children
- Clinical presentation with increased intracranial pressure, cranial nerve palsies, and cerebellar symptoms i.e., nystagmus, diplopia, ataxia
- Mostly occur in children to young adults with peak incidences between 3 and 7 years; median age at diagnosis is 9 years
- Location:
  - ➢ Classic medulloblastomas typically → cerebellar midline, involving the 4th ventricle
  - ➢ Desmoplastic/nodular (D/N) type → cerebellar hemisphere and in the vermis
  - ➢ MBEN type → vermis with involvement of both hemispheres
  - ➢ Large cell/anaplastic (LC/A) type typically → in cerebellar midline and cerebellar structures; LC/A with SHH activation can show lateral localization with extracerebellar extension
- **On imaging**, solid, intensely contrast-enhancing masses (classic and D/N type); large, multinodular lesions with enhancing bunch-of-grapes structures involving the vermis and cerebellar hemispheres (MBENs); heterogeneously contrast-enhancing masses with foci suggestive of necrosis and peritumoral edema (LC/A)

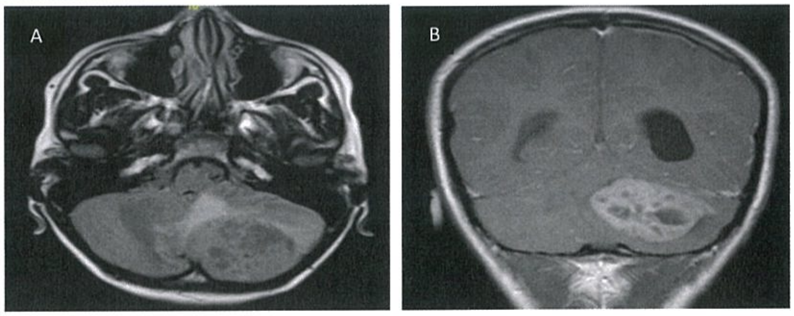

Medulloblastoma. SHH-activated, p53-wildtype, histologically classic type with few small nodules, **GAB1 IHC positive**


Medulloblastoma. SHH-activated, p53-wildtype, histologically classic type with few small nodules, **YAP1 IHC positive**


Medulloblastoma. SHH-activated, p53-wildtype, histologically classic type predominantly with few small nodules, **beta catenin** stain negative, cytoplasmic stain

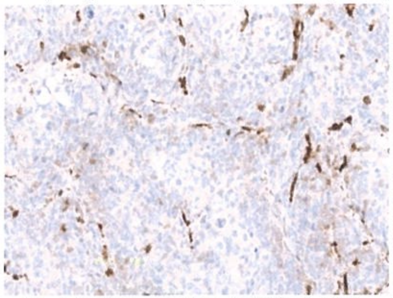

Medulloblastoma. Non-WNT/non-SHH-activated, histologically **anaplastic/large cell type** showing large and anaplastic cells with marked nuclear pleomorphism, numerous mitoses and apoptosis, nuclear molding, and cell wrapping (black star)

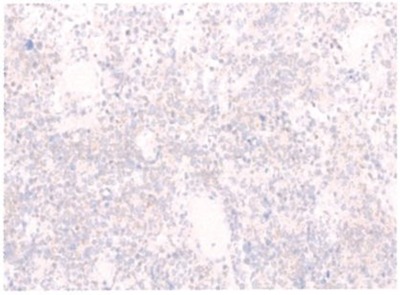

Medulloblastoma. Non-WNT/non-SHH-activated, histologically anaplastic/large cell type, **high Ki-67 proliferation index**



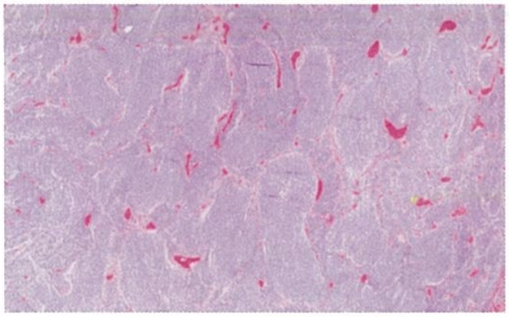
Large complex mass involving dorsal aspect of the left cerebellar hemisphere
A. Axial T1 FLAIR MRI showing a prominent adjacent FLAIR change which crosses the midline into the medial right cerebellar hemisphere
B. Coronal T1 post-contrast MRI showing solid, intensely contrast-enhancing cerebellar mass with multiple non-enhancing areas of presumed cystic change (**Medulloblastoma: SHH-activated, p53-wildtype, histologically classic type with few small nodules**)

- **Immunohistochemistry:**
  - ➢ (+) synaptophysin (diffuse), INSM1, CD56, MAP2, NSE, NeuN (focal)
  - ➢ (-) GFAP
  - ➢ High Ki-67 index
  - ➢ Please see the table below for molecular subgroups' immunophenotypes
- **SHH pathway** → "Sonic hedgehog pathway"
- **WNT pathway** → through CTNNB1 (beta catenin)
- **4 molecular groups:**
  - ➢ WNT-activated
  - ➢ SHH-activated (TP53-wildtype and TP53-mutant)
  - ➢ Non-WNT/non-SHH group 3
  - ➢ Non-WNT/non-SHH group 4
- Differential diagnosis includes other embryonal tumors AT/RT (INI1/BRG1 loss), ETMR (LIN28A positive, C19MC amplified); metastatic small cell neuroendocrine carcinoma in adults (keratin CAM 5.2 positive) and CNS neuroblastoma (FOXR2 activated)
- Clinical staging requires MR of brain and spine, CSF analysis; leptomeningeal/CSF spread (in 20-60%); disseminated disease/CSF spread (M1-M3) → poor prognosis
- Management includes surgical resection/reduction and chemoradiation
- **Main inherited cancer syndromes** with medulloblastoma association are Gorlin syndrome (PTCH1), Li-Fraumeni syndrome (TP53), familial adenomatous polyposis (APC), Rubinstein-Taybi syndrome (CREBBP), and Nijmegen breakage syndrome (NBN [NBS1])

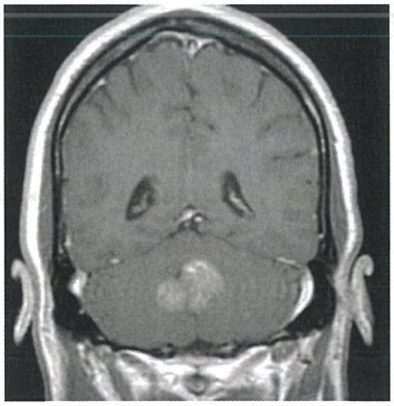

Medulloblastoma. Non-WNT/non-SHH-activated, histologically anaplastic/large cell type, **YAP1 IHC negative**


Medulloblastoma. Non-WNT/non-SHH-activated, histologically anaplastic/large cell type, **GAB1 IHC**

12. EMBRYONAL TUMORS



Medulloblastoma with extensive nodularity (MBEN) with expanded lobular/nodular architecture and narrow internodular strands



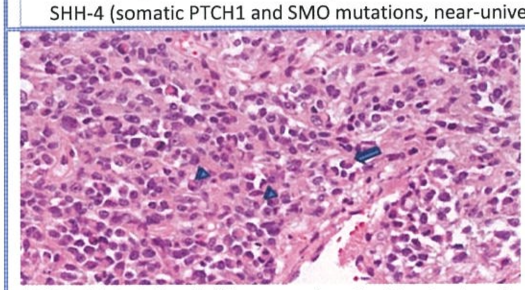
Preoperative coronal T1 post-contrast image shows midline cerebellar, heterogeneously contrast-enhancing mass (non-WNT/non-SHH-activated, histologically **anaplastic/large cell type medulloblastoma)**

MOLECULAR GROUPS OF MEDULLOBLASTOMA

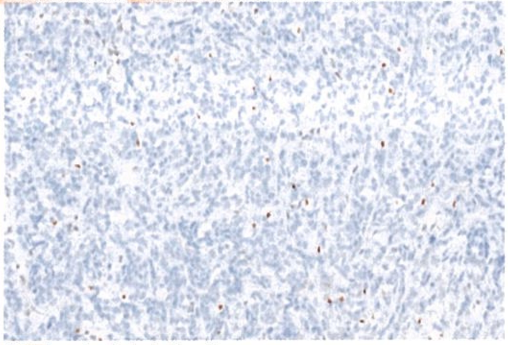
	WNT-Activated	SHH-Activated		Non-WNT/Non-SHH	
		TP53-Wildtype	TP53-Mutant	Group 3	Group 4
Molecular subgroups*		SHH-1 to SHH-4	SHH-3	Group 3/4 subgroups 1-8	
Relative Frequency %	10%	20%	10%	25%	40%
M:F	1:2	1.5:1	3:1	2:1	3:1
Age Group	Children (7-14 years) WNT-alpha (young children); WNT-beta (older children and young adults)	Bimodal distribution; infants (SHH-1 and SHH-2 subgroups) and adults > 19 years (SHH-3 and SHH-4 subgroups)	Children (4-17 years)	Infants/ children (5-15 years)	All ages
Location	Cerebellar midline, CPA, often closer to brainstem	Cerebellar hemispheres (Vermis in infants)	More likely midline than wildtype	Midline cerebellum, Often inferior	
Imaging	Enhance brightly	Solid, intensely contrast-enhancing masses		Heterogenous enhancement	
Histology	Classic	D/N, MBEN > Classic; LC/A (TP53mut)		Classic > LC/A	
Immunophenotype	**Nuclear beta catenin positive**; YAP1 positive	**GAB1 and YAP1 positive;** β-catenin cytoplasmic (nuclear-negative); Strong reactivity for p53 protein in >80% favors TP53 mutation; Reticulin surrounding nodules		GAB1 and YAP1 negative; β-catenin cytoplasmic (nuclear-negative)	
Molecular Genetics^{+}	Somatic mutation in **exon 3 of *CTNNB1***; Monosomy chr 6; *DDX3X* mut	10q loss; Alteration of SHH pathway genes ***(PTCH1**, SUFU, SMO)*	17p loss; MYCN amp	**MYC/MYCN amp;** PVT1::MYC fusion; GFI1, chr 17 alterations; and many others	
Germline Mutation	APC familial Adenomatous Polyposis	PTCH1 Gorlin syndrome, *SUFU, ELP1*	TP53 (Li-Fraumeni syndrome)	Rare BRCA2, PALB2	
Prognosis	**Excellent prognosis** in properly treated children; *TP53* mutations if seen, are somatic and not an adverse prognostic factor	Overall **intermediate prognosis**; **poor prognostic factors** are TP53 mutation, MYCN amp, and LC/A morphology; in infants, favorable features D/N or MBEN		**Poor outcome** associated with MYCN amplification, isodicentric 17q, and metastatic disease at diagnosis	

	(unlike in SHH-activated group)		

* Molecular subgrouping based on DNA methylation or transcriptome profiling
⁺ SHH-1 (somatic or germline SUFU mutation and chromosome 2 gain)
SHH-2 (chromosome 9 loss)
SSH-3 (PT53 and ELP1 mutations)
SHH-4 (somatic PTCH1 and SMO mutations, near-universal U1 and TERT mutations)

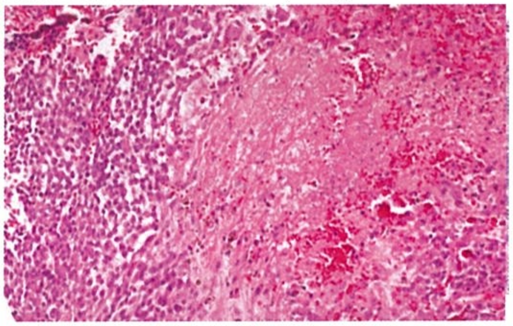


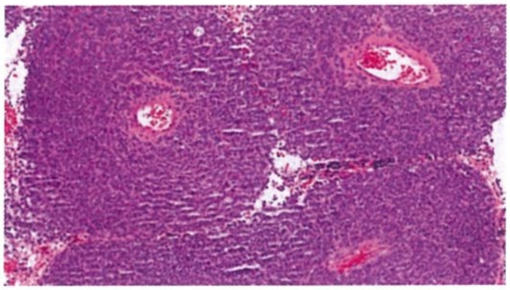
AT/RT. Rhabdoid cells (blue arrowhead) with cytoplasmic inclusions and binucleations (blue arrow)



INI1 loss in rhabdoid cells

AT/RT. Cells show small cell morphology and necrosis





AT/RT. Cells showing fibrillary inclusion (blue arrows and mitoses (blue arrowhead)

AT/RT shows small round blue cells with perivascular arrangement

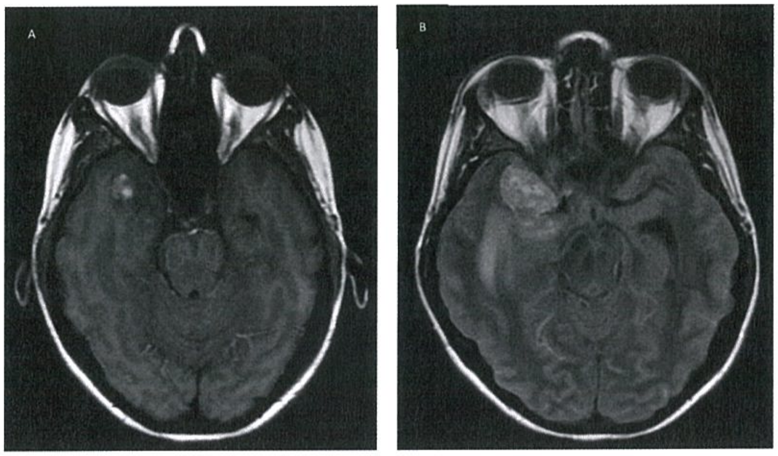
ATYPICAL TERATOID RHABDOID TUMOR (AT/RT)

MORPHOLOGY

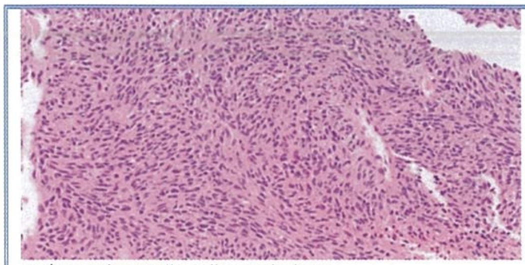
- CNS WHO grade 4, high-grade malignant tumor with poorly differentiated cells
- May show neuroepithelial, epithelial, and mesenchymal differentiation as well as variable rhabdoid features
- Defined by biallelic inactivation of SMARCB1 (INI1/hSNF5/BAF47) or rarely SMARCA4 (BRG1) in less than 5% of cases → part of SWI/SNF chromatin remodeling complex and loss of INI1 by IHC
- Soft, fleshy to firm (in mesenchymal elements), with areas of hemorrhage and necrosis
- Morphologically, **rhabdoid cells** have eccentric nuclei, vesicular chromatin, prominent nucleoli, and abundant eosinophilic cytoplasm with globular inclusions
- Frequently, artifacts of cytoplasmic vacuolation and binucleations are seen
- Undifferentiated, small round blue cell areas, spindle cell/fascicular areas, and less common epithelioid areas with abundant mitotic activity
- Areas of necrosis and hemorrhage are common

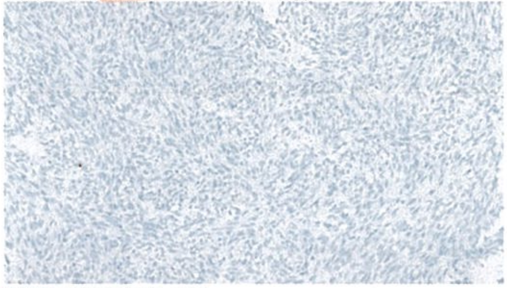
OTHER HIGH YIELD POINTS

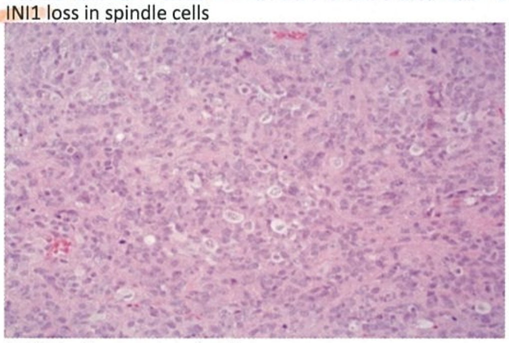
- Clinical presentation with nonspecific signs of increased intracranial pressure and site-specific neurologic signs (e.g., cranial nerve palsy, hemiplegia etc.)
- Slight male predominance (M:F ratio 3:2 to 2:1), accounts for 10% of CNS tumors in infants and 1-2% in pediatric patients
- On imaging, variably enhancing with frequent hemorrhage and necrosis
- CSF dissemination is common (in 1/3 of patients at presentation)
- Clinical staging uses MRI with contrast agent and CSF cytology
- **3 molecular subtypes of AT/RT:**
  - ➢ AT/RT-SHH (44% of AT/RTs)
  - ➢ AT/RT-TYR (34% of AT/RTs)
  - ➢ AT/RT-TYR (22% of AT/RTs)



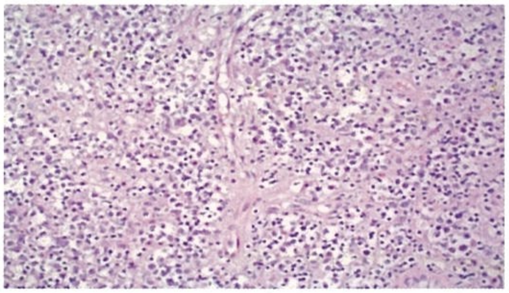
A. Axial T1SE sequence MRI shows mixed solid and cystic areas in homogeneously enhancing mass in the right frontal region and lobulated cystic components in the anterior aspect with fluid-fluid levels
B. Axial T2 FLAIR MRI shows extensive surrounding vasogenic edema


AT/RT with spindle cell morphology


INI1 loss in spindle cells


AT/RT with vacuolated cells

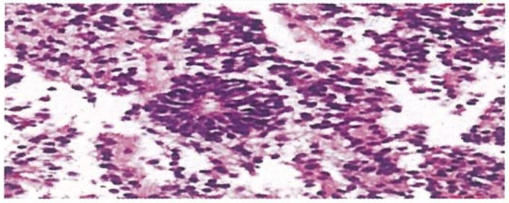
Sellar AT/RT showing vacuolated cells



- IHC: Nuclear loss of INI1; (+) EMA, SMA (in rhabdoid cells); (+/-) GFAP, synaptophysin, CK
- Ki-67 usually > 50%
- If INI1 and BRG1 are intact, then should be reported as **"CNS embryonal tumor with rhabdoid features"**
- Differential diagnosis include medulloblastoma, other CNS embryonal tumor, choroid plexus carcinoma, and anaplastic ependymoma; ancillary diagnostic studies are important in making distinction as mentioned above
- **Familial cases arise with tumor predisposition syndrome 1 (SMARCB1) or 2 (SMARCA4),** significantly higher with SMARCA4-deficient tumors
- Ultra-structurally, most prominent finding is cytoplasmic whorls of intermediate filaments
- Treatment is total surgical resection and chemotherapy regimen with stem cell rescue and radiation
- Immune checkpoint inhibitors → potential therapeutic options in AT/RT-MYC and AT/RT-TYR molecular subtypes
- Prognosis is poor with worse overall survival associated with subtotal resection of tumor, delayed radiotherapy, CSF seeding at diagnosis, and young age at diagnosis (< 3 years)
- Both the COG ACNS333 trial and the EU-RHAB study demonstrated the prognostic significance of molecular group; a non-AT/RT-TYR molecular profile was recognized as independent negative prognostic marker
- In the COG trial, the 4-year survival rate was reported to be higher in AT/RT-SHH subtype tumors

MOLECULAR SUPTYPES OF AT/RTs

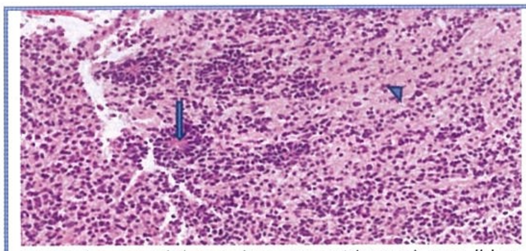
	AT/RT-SHH	AT/RT-TYR	AT/RT-MYC
Age	2-6 years	0-1 years	> 3 years
Location	Supratentorial > infratentorial	Infratentorial > supratentorial	Supratentorial > infratentorial
SMARCB1/Ch.22 Alterations	Point mutation of SMARCB1	Mutation in 1 allele of SMARCB1; long-stretched deletions of ch. 22 removes the 2nd allele of SMARCB1	Homozygous /focal loss of SMARCB1
Methylation Status	Hypermethylation	Hypermethylation	Hypomethylation
Gene Expression Level Pathway Deregulation	Genes involved in **axonal guidance and neurogenesis** overexpress proteins involved in SHH signaling pathways (GLI2, BOC, PTCHD2) and NOTCH signaling pathways (ASCL1, CBL, HES1)	Upregulation of proteins in **melanosome pathway** including tyrosinase, BMP signaling, melanogenesis (TYR, TYRP, MIT), and mesenchymal genes (OTX2, PDGFRB, BMP4)	Expression of **MYC oncogene and HOX cluster genes**; rare spinal AT/RTs and sellar AT/RTs in adults are AT/RT-MYC type


ETMR shows multilayered rosettes with true lumen, a defining feature

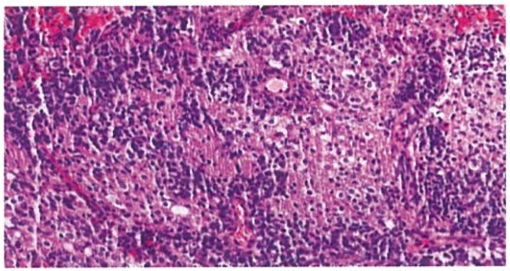
EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES (ETMR)

MORPHOLOGY

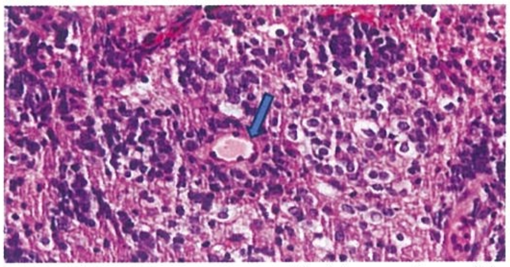
- Rare embryonal neoplasm of young children (< 4 years)
- **Histologically CNS WHO grade 4;** previously with 3 morphologic patterns:
  - Embryonal tumor with abundant neuropil and true rosettes (ETANTR)
  - Ependymoblastoma
  - CNS Medulloepithelioma



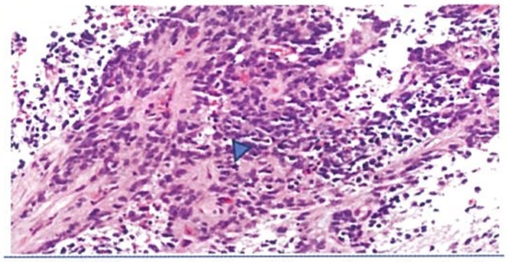
ETMR shows multilayered rosettes with true lumen (blue arrow) combined with fibrillar neuropil (blue arrowhead)



ETMR-C19MC-altered with multilayered rosettes, of which the outer layer of rosettes is merging with embryonal/small cells (small cell phenotype)



Rosettes have prominent internal limiting membrane (blue arrow) with eosinophilic granular band produced by terminal bars adjacent to lumen. Lumen is lined by cilia and blepharopalsts. Such structures and external limiting membranes are absent in ependymoma rosettes



ETMR-C19MC-altered with multilayered rosettes showing focal areas of ependymoblastic rosette-like morphology with intraluminal mitoses (blue arrowhead)

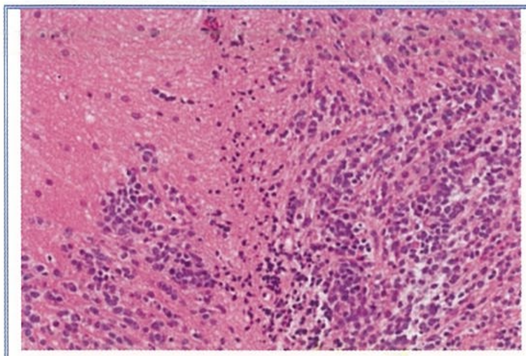
3 MORPHOLOGIC PATTERNS OF ETMR

	ETANTR	Ependymoblastoma	CNS Medulloepithelioma
Morphology	The presence of **"multilayered rosettes" with true lumina** and abundant neuropil	**"Ependymoblastic" rosettes with true lumina**; outer layers of rosettes seem to merge with embryonal cell histology; lacks abundant neuropil-like background and ganglion cells	**"Multilayered rosettes"-like structures** with **papillary, tubular, or trabecular arrangements of primitive neuroepithelium** with PAS-positive membranes; sheets of embryonal cells away from tubular or papillary structures; **rare mesenchymal differentiation** and melanin pigmentation
IHC and Special Stains for Rosettes	**CD99 or D2-40 positive in basal bodies of cilia (blepharoplasts)** on the apical regions of tumor cells, lining the central lumen of **"true rosettes"**	**CD99 or D2-40 positive in basal bodies of cilia (blepharoplasts)** **EMA (weakly positive in rosettes**, rare dot-like positivity) differentiates it from **anaplastic ependymoma** (EMA strongly positive in dot-like pattern in microlumina of perivascular pseudorosettes, composed of single layer of mitotically inactive cells)	**Cilia and blepharoplasts are absent** on the luminal surface of the tubules of primitive epithelium **Collagen IV and PAS** stain basement membrane surrounding neural tube-like structures

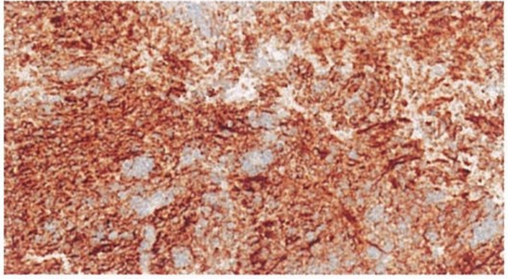
- Now unified under a single terminology "ETMR-C19MC-altered" (rare DICER mutation/DNA methylation profile aligned ETMR; molecular subtypes), as currently defined by the WHO
- Grayish pink, soft, fleshy, somewhat circumscribed with areas of necrosis, hemorrhage; sometimes cystic changes and calcifications
- Morphologically, **defining feature is multilayered rosettes** (pseudostratified neuroepithelium with a central lumen)
- Neuroepithelial cells are mitotically active toward the lumen with prominent internal limiting membrane

OTHER HIGH YIELD POINTS

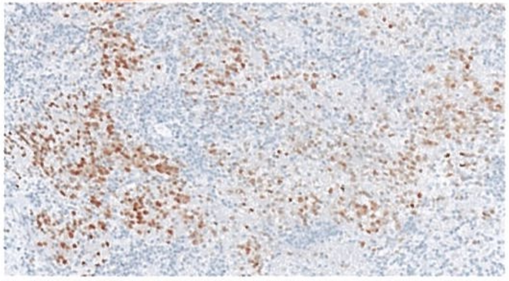
- Clinical presentation with **raised intracranial pressure** and occasionally seizures
- Locations: Intracranial, supratentorial > infratentorial, cerebral hemispheres, brainstem, or cerebellum; rarely spinal cord
- On imaging, variably enhancing tumor with mass effect and occasional cysts or calcifications; mimics diffuse midline glioma in case of brainstem ETMRs



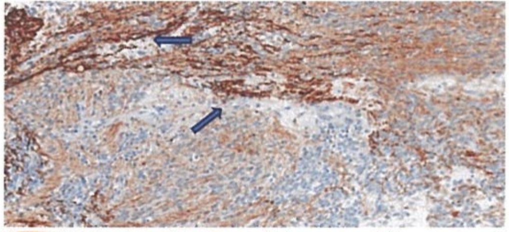
ETMR shows areas of neuropil and apoptosis



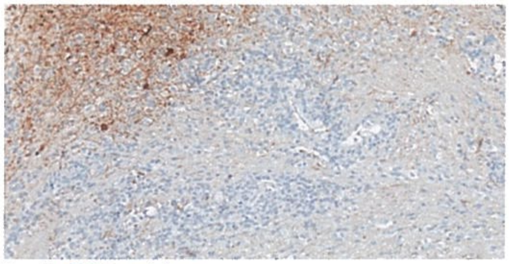
Positive for synaptophysin in neuropil



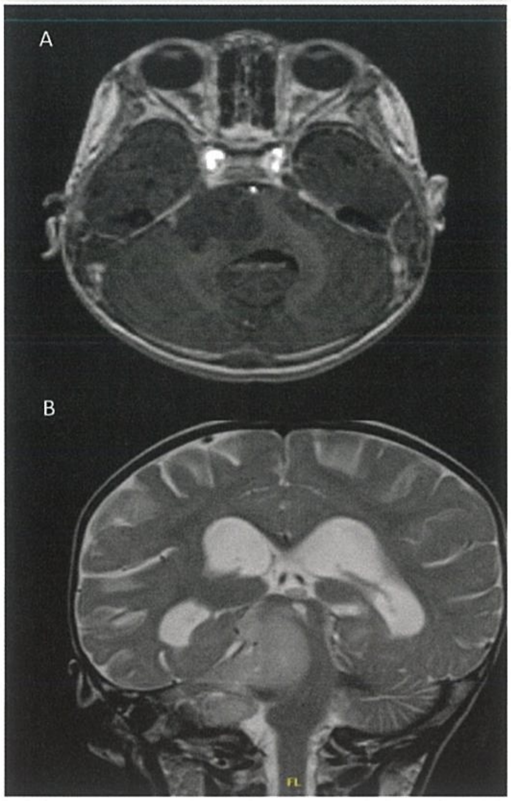
Variably NeuN-positive neurocytic tumor cells in neuropil-rich regions



Neurofilament-positive axons (blue arrows) form neuropil



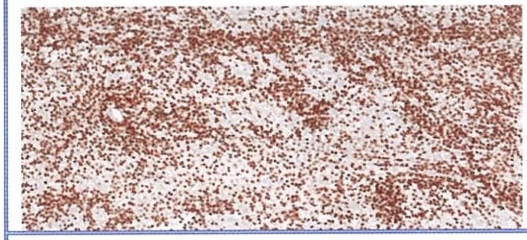
Focally GFAP positive



A. Axial FLAIR T1 MRI
B. Coronal T2 MRI with focal T2 hyperintensity shows intra-axial brainstem mass lesion extending into the right cerebral peduncle, medial right temporal lobe, and right brachium pontis

- Most localized (75%), prognosis is poor with local recurrence and occasional extradural and leptomeningeal spread with widespread CSF metastases
- IHC: Positive for synaptophysin and NeuN in neuropil-rich areas
- Variable CKs, EMA (weakly positive), CD99, GFAP (focal positivity), and D2-40 (positive in rosettes)
- **INI1 is retained** in ETMR, whereas INI1 expression is lost in AT/RT
- Intraocular medulloepithelioma and sacrococcygeal ependymoblastoma are morphologically similar to ETMR, but they are strikingly different from ETMR on a molecular basis
- **LIN28A immunostaining** consistently positive in ETMR-C19MC-altered cases (differentiate ETMR from other embryonal tumors)
- No amplification of MYC gene locus by interphase fluorescence in-situ hybridization (FISH)
- **C19MC (microRNA) upregulation via** amplification or rearrangement of 19q13.42
- Chromosome 2 gain, rare DICER1 mutations (in LIN28 positive cases without C19MC amplification)
- Overall survival prolongation with gross total resection, radiotherapy, and high-dose chemotherapy
- Aggressive clinical course with average survival time of 12 months after intensive combination therapies
- Adverse outcome is associated with metastatic disease at presentation and brainstem tumors; post-treatment neuronal differentiation has been proposed to have a favorable outcome

INI1 retained in ETMR



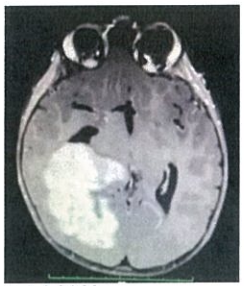
CNS NEUROBLASTOMA, FOXR2-ACTIVATED

MORPHOLOGY

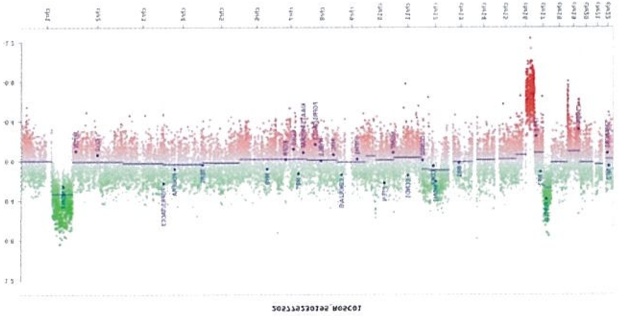
- CNS embryonal neoplasm, **CNS WHO grade 4** with variable neuroblastic and/or neuronal differentiation, including foci of ganglion cells and neuropil-rich stroma
- Soft, well-circumscribed, pink mass; firm and tan if desmoplastic
- Microscopically, variable patterns include sheets of poorly differentiated cells with high N:C ratio and hyperchromatic nuclei, neuroblastic rosettes (Homer Wright), and palisades of embryonal cells
- Abundant mitoses and areas of necrosis
- Variable infiltration of CNS parenchyma
- Focal formation of ganglion cells with cells showing neurocytic differentiation (known as ganglioneuroblastoma)

OTHER HIGH YIELD POINTS

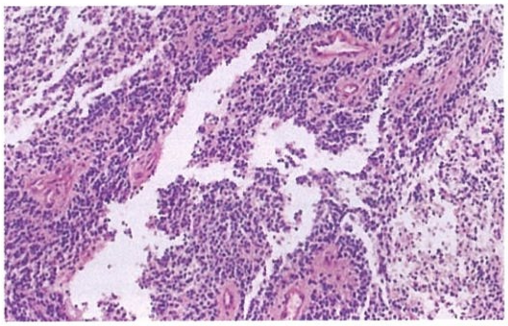
- Clinical presentation data are limited, leptomeningeal spread may develop in some cases
- Occurs in childhood, F > M
- Represents 10% of tumors, previously known as "primitive neuroectodermal tumor (PNET) of CNS"
- Location: **Cerebral hemispheres,** intraventricular location (rare)
- Imaging: **Well-circumscribed mass** in cerebral hemisphere, heterogeneous enhancement of solid component ± prominent **cystic component**
- IHC: **(+) OLIG2**, MAP2, SOX10, TTF1/NKX2-1; synaptophysin positivity more prominent in neurocytic areas and areas of ganglion cell differentiation; Ki-67 proliferation index is high; (-) GFAP, vimentin
- Molecular pathology: **Complex FOXR2 alterations** chr Xp11.21; **gain of chromosome 1q**
- Diagnosis is complex, requiring NGS and **DNA methylation**
- Treatment: Surgery with adjuvant chemoradiation, responds better in comparison to other embryonal neoplasms but data are limited



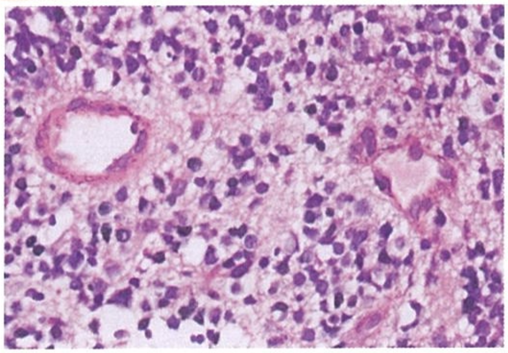
MRI showing a solid, contrast-enhancing neuroblastoma in the right central parietal lobe



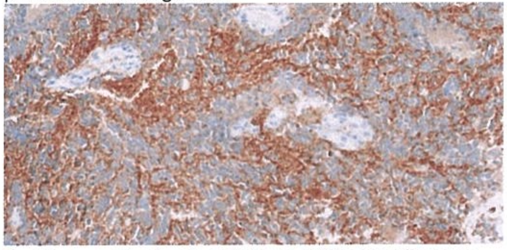
Copy number plot shows 1q gain/16q loss; Pictures courtesy: Felipe D´Almeida Costa, MD



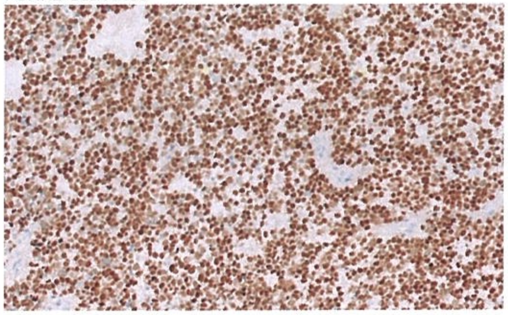
CNS neuroblastoma, FOXR2-activated showing small blue round tumor cells in a fibrillary background



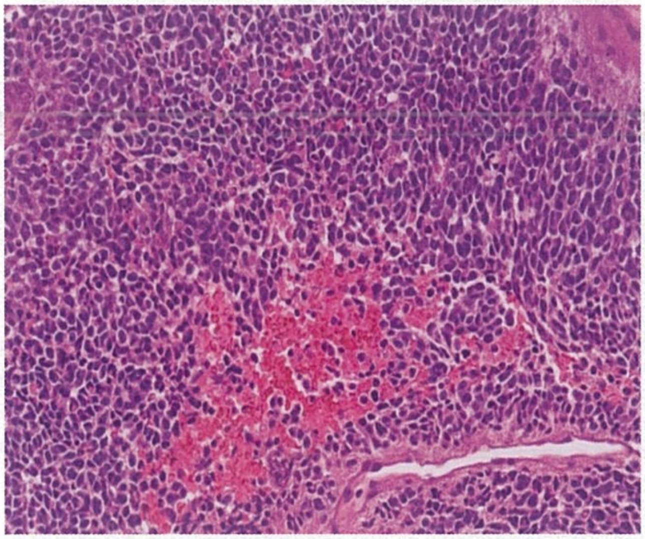
Neuroblastoma showing perinuclear clearing and perivascular arrangement



Positive synaptophysin staining in CNS neuroblastoma, FOXR2-activated



Diffuse positive staining for OLIG2



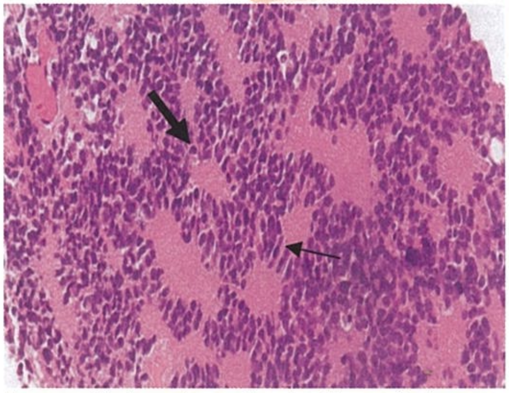
PINEAL TUMORS

LAKSHMI RAMACHANDRAN NAIR, MD

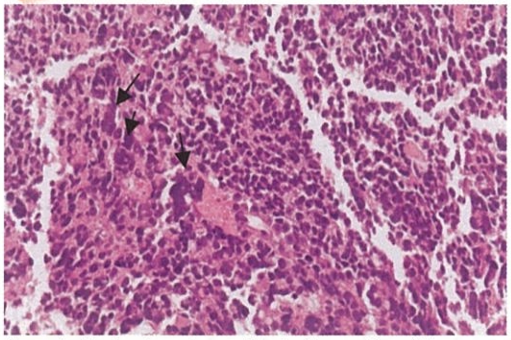
13. PINEAL TUMORS

PINEAL TUMORS

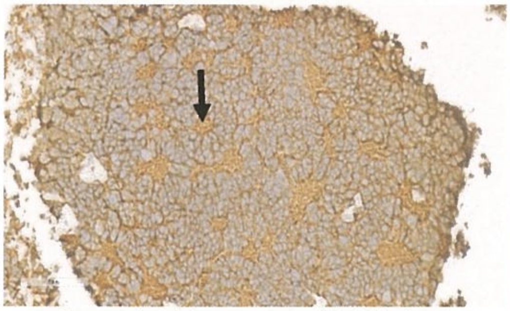
Pineocytoma showing many pineocytomatous rosettes



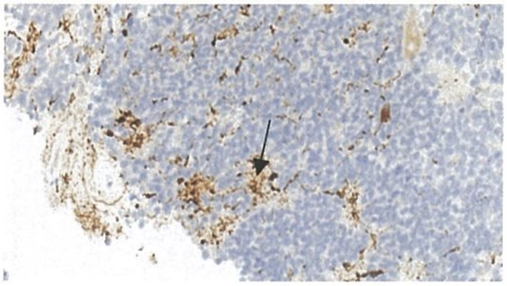
Pleomorphic, hyperchromatic cells with ganglionic differentiation



Synaptophysin strongly positive in the center of the rosettes



Neurofilament highlighting terminal "club-like" ends



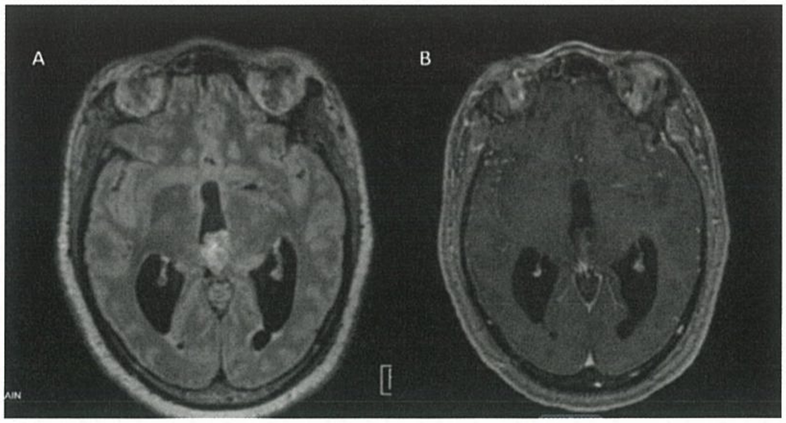
PINEOCYTOMA (CNS WHO GRADE 1)

MORPHOLOGY

- Composed of sheets or poorly formed lobules of **small, monomorphic, mature cells** with fine chromatin and occasional micronucleoli
- Round clusters of nuclei with a central fine fibrillary zone called **"pineocytomatous rosettes"**
- Presence of pineocytomatous rosettes and absence of well-defined lobular architecture is a clue to differentiate from normal pineal gland tissue that may also have bland tumor cells
- Ganglionic differentiation with large, hyperchromatic, pleomorphic cells with irregular nuclear contours can occasionally be found. Not considered worrisome in an otherwise low-grade pineocytoma
- **Mitoses are rare** to absent, and **Ki-67 counts are low (< 1%)**
- Gross exam: Firm, grayish-tan well-circumscribed mass

OTHER HIGH YIELD POINTS

- Clinically presents with Parinaud syndrome and increased intracranial pressure symptoms (headache, nausea, papilledema, and vomiting)
- Most common in the 4th decade of life with slight female predominance
- May compress surrounding structures (brainstem, cerebellum) or protrude into the 3rd ventricle
- Excellent prognosis with more than 90% 5-year survival rate
- Gross total resection is the most important prognostic factor
- IHC: (+) **synaptophysin**, NSE, **neurofilament**, **CRX**, chromogranin (variable)
- Synaptophysin and neurofilament also highlight the "club-like" end terminals in the center of pineocytomatous rosettes
- Molecular: No recurrent genetic alterations; distinct DNA methylation profile (similar to normal pineal gland tissue)

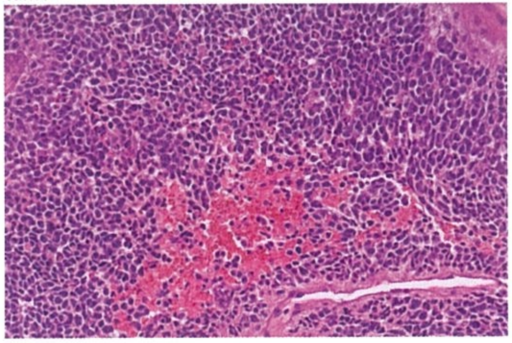


A. Axial T2 FLAIR MRI showing a FLAIR hyperintense pineal region mass
B. Axial T1 post-contrast MRI showing a faintly rim-enhancing pineal mass

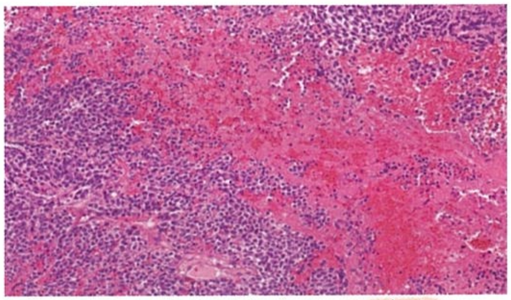
Path Presenter

13. PINEAL TUMORS

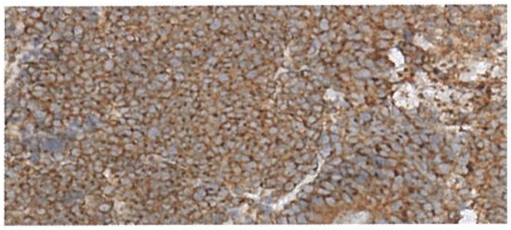
Hypercellular, hyperchromatic, small blue round cell tumor



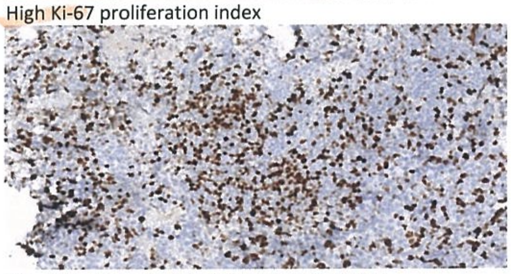
Extensive areas of hemorrhage and necrosis



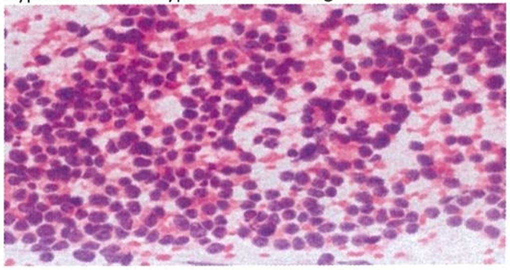
Diffuse strong positive staining for synaptophysin



High Ki-67 proliferation index



Pineoblastoma smear preparation showing hyperchromatic atypical cells with high N:C ratio



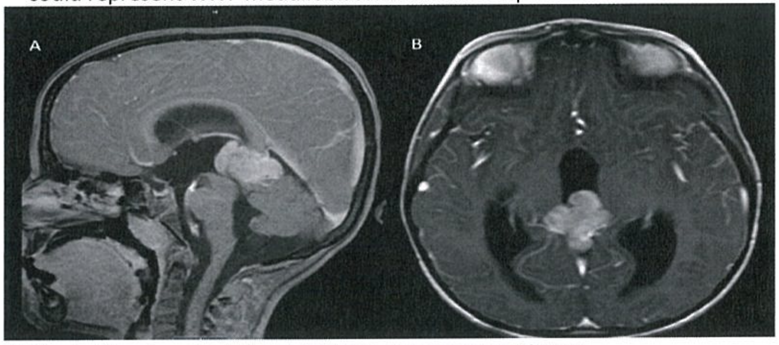
PINEOBLASTOMA (CNS WHO GRADE 4)

MORPHOLOGY

- Composed of **small round blue cells forming dense sheets; high N:C ratio**
- **Brisk mitoses**, apoptotic debris, necrosis, and hemorrhage usually present
- Homer Wright and Flexner-Wintersteiner rosettes may occasionally be seen (pineocytomatous rosettes are absent)
- May resemble another embryonal neoplasm on H&E, so confirmation of pineal location is crucial
- Gross exam: Soft or friable mass with areas of hemorrhage or necrosis

OTHER HIGH YIELD POINTS

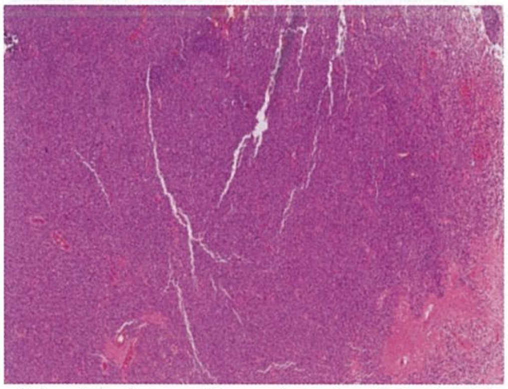
- May be present at any age but usually **affects children** with a slight female predominance
- Rapid growth with local invasion or secondary mass effect in adjacent structures as well as hemorrhage and cystic changes within the tumor are common
- **CSF spread** with drop metastasis along the spinal cord and leptomeningeal seeding can be seen
- IHC: (+) synaptophysin and NSE (expression can be variable)
- Differential diagnosis includes medulloblastoma (CRX-negative), AT/RT (INI1 or BRG1 lost), ETMR (pineoblastomas are LIN28A negative); **high Ki-67** index
- Association with familial retinoblastoma (RB1 mutation) and DICER1 germline mutation
- **4 distinct molecular subgroups** based on methylation profiling:
  - ➢ miRNA processing-altered_1: Associated with DICER1 syndrome
  - ➢ miRNA processing-altered_2: Associated with DICER1 syndrome
  - ➢ RB1-altered (pineal retinoblastoma): Associated with hereditary retinoblastoma
  - ➢ MYC/FOXR2 activated
- Metastatic spread is common for the RB1-altered subgroup
- miRNA processing-altered_2 subgroup shows excellent prognosis
- Aggressive clinical course with varying survival rates depending on molecular subtype
- Overall **short survival** except for miRNA processing-altered_2 subgroup
- A novel WNT-activated embryonal tumor of the pineal region with a good prognosis is reported; not clear if this is a subgroup of pineoblastoma and could represent WNT-medulloblastoma in an ectopic location



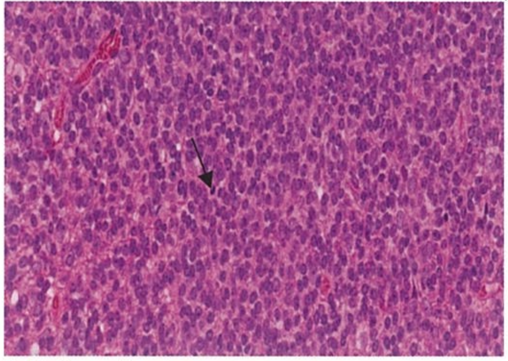
MRI brain T1 post-contrast showing a large, enhancing pineal mass
A. Sagittal view
B. Axial view

Path Presenter

Hypercellular neoplasm with diffuse, sheet-like growth



Mild nuclear pleomorphism and occasional mitotic activity



Path Presenter

PINEAL PARENCHYMAL TUMOR OF INTERMEDIATE DIFFERENTIATION (PPTID; CNS WHO GRADE 2-3)

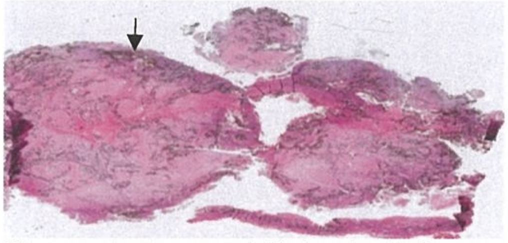
MORPHOLOGY

- Composed of **moderate to hypercellular** small monomorphic cells with **intermediate differentiation** between the tumor cells of pineocytoma and pineoblastoma
- 2 distinct architectural patterns:
  - Diffuse (oligodendroglioma or neurocytoma-like)
  - Lobulated (lobules delineated by vessels)
- **Mild to moderate nuclear pleomorphism** and small to moderate amounts of eosinophilic cytoplasm
- **Mitoses** are not very elevated like pineoblastoma, **> 6/10 HPF**
- Gross exam: Well-circumscribed tumor (similar to pineocytoma)

OTHER HIGH YIELD POINTS

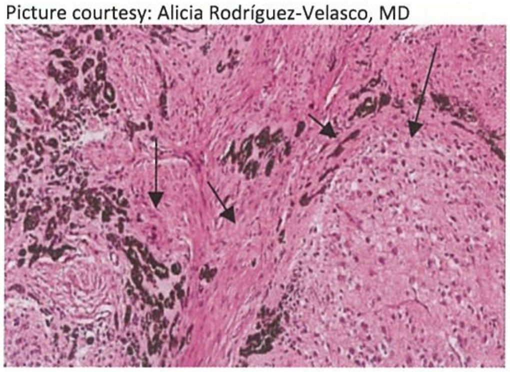
- Rare tumor; affects both **children and adults** with a mean age of 41 years
- **Intermediate behavior** and prognosis between pineocytoma and pineoblastoma
- IHC: (+) synaptophysin and CRX; **neurofilament** expression is **variable**
- Pineocytoma, neurocytoma, and oligodendroglioma are top histologic differential diagnoses
- Histologic grading criteria are not defined by WHO; however, **low-grade PPTIDs** have low mitotic counts, low Ki-67 (< 5%), and retained neurofilament expression in many tumor cells as compared to **high-grade PPTIDs** which show loss of or rare tumor cells with neurofilament expression, high mitotic counts, and elevated Ki-67 (> 5%)
- Molecular: **Small in-frame insertions in KBTBD4** are a characteristic feature; **distinct DNA methylation profile** with 2 subgroups
  - PPTID-A
  - PPTID-B

8-month-old patient with a solid, highly pigmented tumor



Glioneuronal nests surrounded by large bands of epithelioid cells with abundant melanin and stromal cells with rhabdomyoblastic characteristics

Picture courtesy: Alicia Rodríguez-Velasco, MD



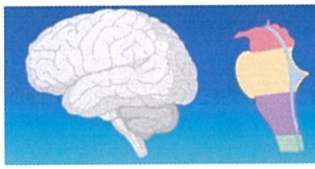
PINEAL ANLAGE TUMOR

MORPHOLOGY

- **Biphasic** tumor composed of **neuroectodermal component and heterologous mesenchymal components**
- Neuroectodermal component could be pineoblastoma-like, ganglionic/glioneuronal, and/or epithelioid cells with melanin
- Ectomesenchymal components could be cartilage and/or muscle

OTHER HIGH YIELD POINTS

- **Very rare** and **aggressive** pineal neoplasm
- Hypothesized to be a subtype of **pineoblastoma**
- No CNS grade assigned as of now in the CNS 5 WHO classification (< 2021)
- Clinically presents with variable symptoms such as hydrocephaly, headaches, nausea, vomiting, ataxia, lethargy, or seizures
- Main differential diagnoses: Teratoma (includes components of the endodermal layer), medulloblastoma with myogenic and melanotic differentiation (predominance of small blue round cells and, if melanin is observed, it does not surround nests of neuroglial tissue but rather forms clumps or clusters), and melanotic neuroectodermal tumor of infancy/melanotic progonoma/retinal anlage tumor (no mesodermal component such as muscle or cartilage present)
- Detailed information is not available to comment on molecular and DNA methylation profile of this tumor



13. PINEAL TUMORS

PAPILLARY TUMOR OF THE PINEAL REGION (CNS WHO GRADE 2-3)

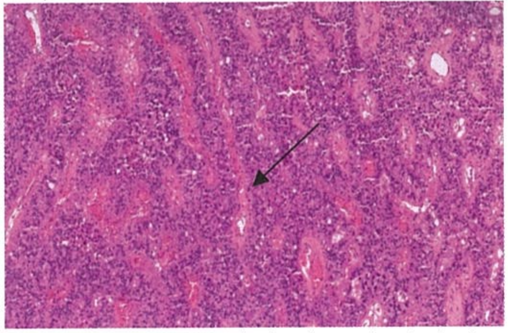
MORPHOLOGY

- Composed of varying proportions of **solid and papillary** areas with sharp demarcation from adjacent normal pineal gland
- Papillary areas have pseudostratified epithelium showing **columnar to cuboidal epithelial-like cells**
- Solid areas are diffuse tumor sheets occasionally showing ependymoma-like rosettes or tubes
- **Cytoplasmic clearing**, hyalinized blood vessels, and necrotic foci could be present
- Mitoses and Ki-67 index are moderate, no defined grading criteria for WHO grade 2 vs. 3

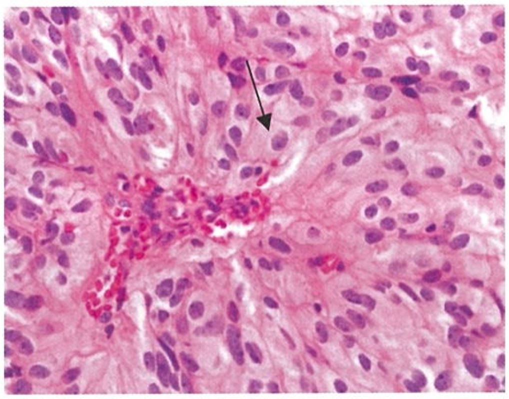
OTHER HIGH YIELD POINTS

- Rare tumor seen in children and adults
- IHC: (+) cytokeratin (mainly **CK8/18**), **S100**, **CD56**, transthyretin, and SPDEF
- IHC: (-) GFAP, neurofilament, CRX
- Recurrent chromosomal abnormalities include **gain on chromosomes 4 and 9** and **loss from chromosome 10**
- Main differential diagnoses are metastatic adenocarcinoma, pineal parenchymal tumors (CRX and synaptophysin positive, CK8/18 negative), ependymoma (GFAP positive), and choroid plexus tumors (Kir7.1 and E-cadherin positive, CD56 negative)
- Local recurrences are common; gross total resection and younger age are associated with better overall survival
- **Distinct DNA methylation profile** with 2 subgroups
  - ➢ PTPR-A
  - ➢ PTPR-B

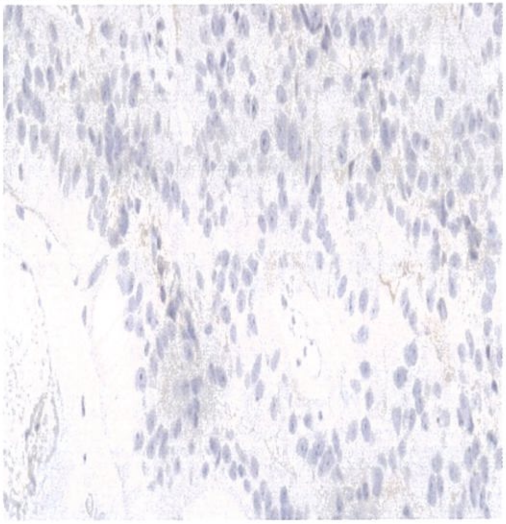
Low power showing predominantly papillary architecture

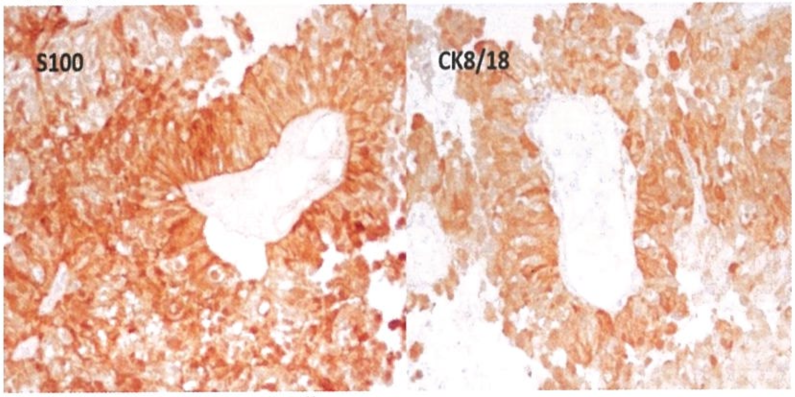


Ovoid nuclei with micronucleoli and cytoplasmic clearing



GFAP showing negative staining





Picture courtesy: Pepe Jimenez Heffernan, MD

Path Presenter

DESMOPLASTIC MYXOID TUMOR OF THE PINEAL REGION, SMARCB1-MUTANT

MORPHOLOGY

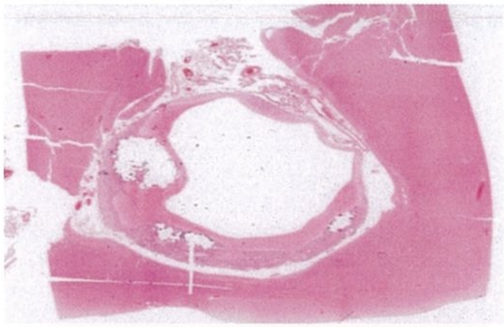
- Composed of cords of **spindled to epithelial cells in a loose myxoid matrix with admixed dense collagen**
- Small to medium cells and bland cells with **no overt histologic features of malignancy**
- Desmoplasia and fibrosis of blood vessels are seen
- **Mitoses are rare**

OTHER HIGH YIELD POINTS

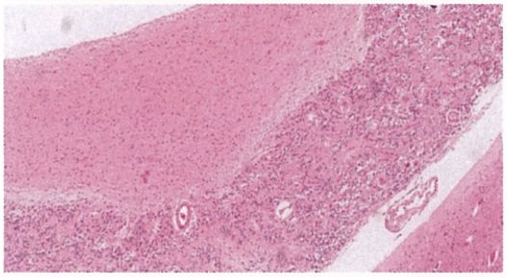
- Only 7 known reported cases, with median age of 40
- IHC: **Loss of SMARCB1 (INI1) nuclear expression** but no histologic features of malignancy as seen in AT/RT
- No CNS grade assigned as of now in the CNS 5 WHO classification (< 2021)
- Genetic alteration in SMARCB1 on **22q11**
- DNA methylation shows distinct clustering, close to AT/RT-MYC subgroup
- **No recurrence or metastasis** in the reported 7 cases after gross total resection

13. PINEAL TUMORS

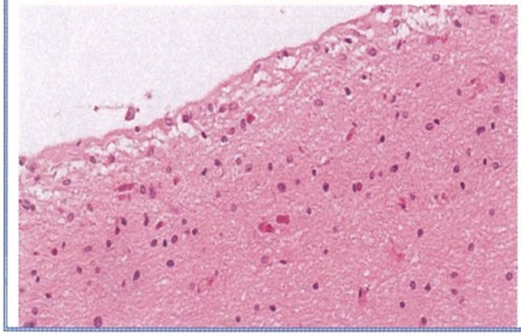
Pineal cyst from an autopsy specimen



Cyst wall with prominent glial and pinealocyte layers



Piloid gliosis with many Rosenthal fibers



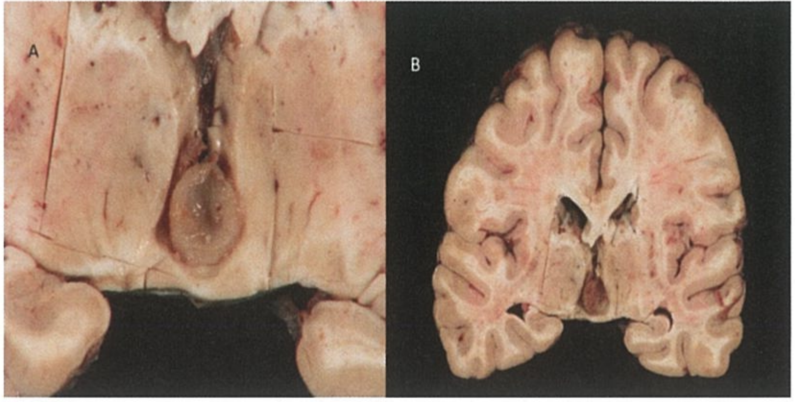
PINEAL CYST

MORPHOLOGY

- Grossly a **circumscribed, midline cystic** mass **in pineal region** with a smooth cyst wall
- 3 layers of varying thickness are seen in the cyst wall
  - **Outer thin fibrous layer** composed of leptomeningeal fibroconnective tissue
  - **Middle layer** composed of a rim of **compressed pinealocytes**
  - **Inner glial layer** composed of sparse reactive **astrocytes** and many **Rosenthal fibers**
- Occasional hemosiderin and degenerative atypia

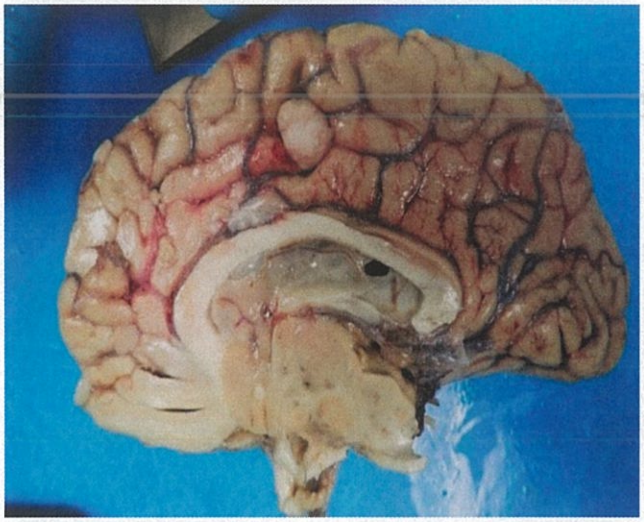
OTHER HIGH YIELD POINTS

- Found in 2-3% of population and usually an incidental finding in autopsy
- Top differential diagnoses include pineocytoma and pilocytic astrocytoma



Gross images of a large pineal cyst from an autopsy specimen
Picture courtesy: Robert Schmidt, MD

Path Presenter



MENINGIOMA

ANNA MATHEW, MD
SILVIA J. HERNANDEZ, MD
JOLEE SUDDOCK, DO

Subtipos

① Meningotelial
② Fibroso
③ Transicional
④ Psamomatoso
1° ⑤ Angiomatoso
⑥ Microquistico
⑦ Secretor
⑧ Linfoplasmocitico
⑨ Metaplasico

---

⑩ Cordoide
2° ⑪ Celulas claras
⑫ Atípico

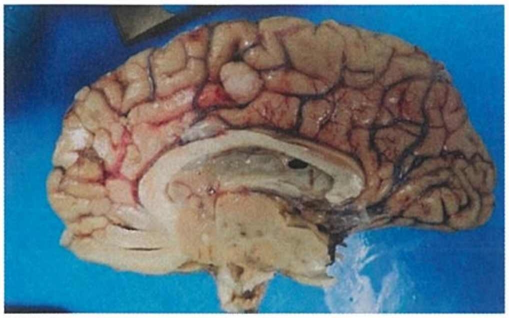
---

⑬ Papilar
3° ⑭ Rabdoide
⑮ Anaplasico

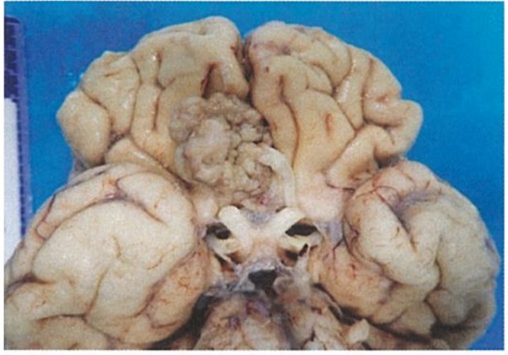
14. MENINGIOMA

MENINGIOMA

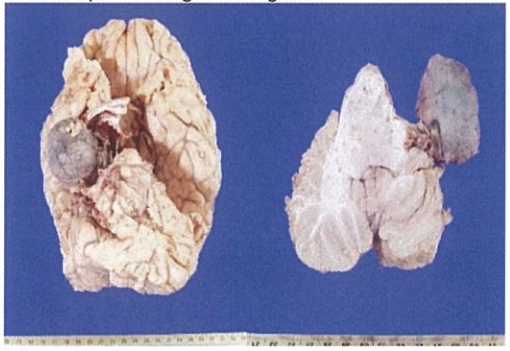
Dural-based lesion (falx)
Picture courtesy: Raquel Yokoda, MD



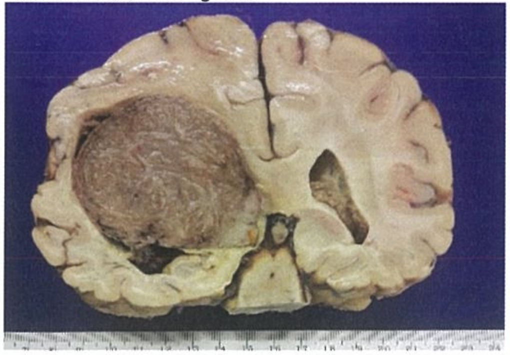
Olfactory groove meningioma
Picture courtesy: Jamie Walker, MD



Cerebellopontine angle meningioma



Intraventricular meningioma



Transitional meningioma with a nodular, rubbery surface

GENERAL FEATURES

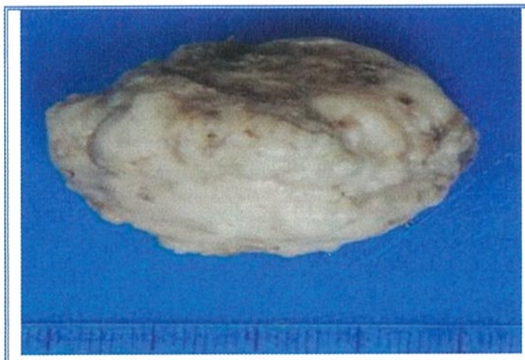
MORPHOLOGY

- Slow-growing tumors composed of meningothelial cells with oval nuclei, delicate chromatin, frequent nuclear pseudoinclusions, whorls, and psammoma bodies
- Gross: Commonly solid, globular, circumscribed masses that are firm and rubbery
  - ➢ Lobulated or bilobed
  - ➢ Flat, carpet-like (en plaque) pattern
  - ➢ Gritty (psammomatous subtype, especially those in spinal locations)
  - ➢ Atypical and anaplastic types often attached to brain
- Histology**: 15 subtypes**; most have a benign clinical course and correspond to CNS WHO grade 1. Higher-grade histologic features may occur in any of the morphologic subtypes
  - ➢ Common histologic subtypes: Meningothelial, fibrous, and transitional
  - ➢ Borders are generally sharp and pushing (cortical invasion in higher-grade tumors)

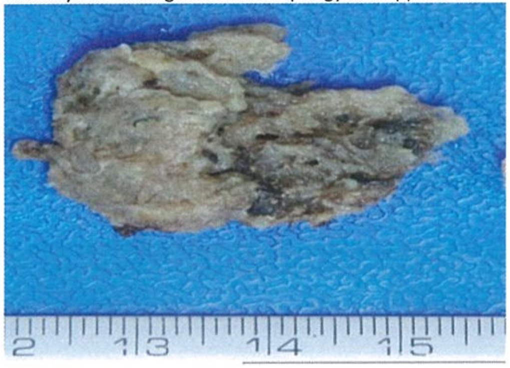
CNS WHO GRADE 2 (Atypical)
4-19 mitoses in 10 HPF (OR)
Chordoid or clear cell subtype (OR)
Brain invasion (OR)
At least 3 of the following: ➢ Increased cellularity ➢ Small cell formation ➢ Prominent nucleoli ➢ Sheeting architecture (sheet-like or uninterrupted, patternless growth) ➢ Spontaneous necrosis
CNS WHO GRADE 3 (Anaplastic)
20 or more mitoses in 10 HPF (OR)
Frank anaplasia (sarcoma, carcinoma, or melanoma-like appearance) (OR)
TERT promoter mutation (OR)
Homozygous deletion of CDKN2A and/or CDKN2B

OTHER HIGH YIELD POINTS

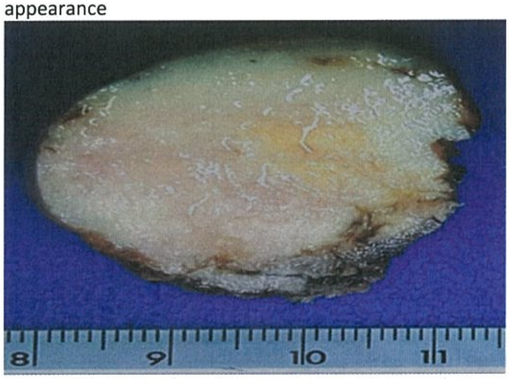
- Most likely developed from **meningothelial cells of the arachnoid mater**
- Most common brain tumor **in adults**, yet, uncommon < 20 years; more common in females than males
- Etiology: Most are sporadic; increased risk with **ionizing radiation** (greater when exposed in childhood), neurofibromatosis type 2, germline mutations associated with clear cell histologic type (SMARCE1), and rhabdoid histologic type (BAP1)
- Location: Typically arise in **intracranial, intraspinal, or orbital locations**
  - ➢ Intracranial: **Cerebral convexities** (commonly parasagittal in association with falx and/or venous sinuses)
  - ➢ Intraventricular (rare)
  - ➢ Optic nerve sheaths
  - ➢ Olfactory grooves
  - ➢ Sphenoid ridges
  - ➢ Parasellar/suprasellar regions
  - ➢ Clivus
  - ➢ Foramen magnum
  - ➢ Petrous ridges
  - ➢ Tentorium



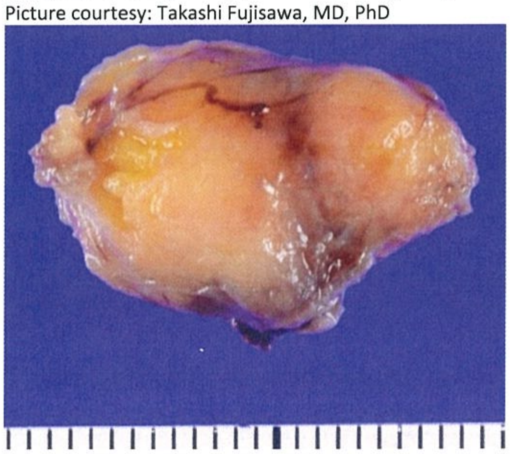
Microcystic meningioma with a spongy-like appearance



Lymphoid-plasmocytic meningioma with a soft, whitish appearance

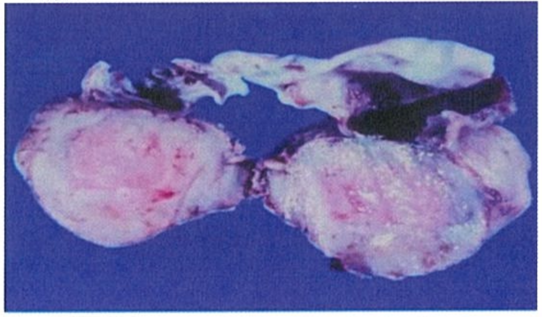


Metaplastic meningioma (lipomatous meningioma)
Picture courtesy: Takashi Fujisawa, MD, PhD

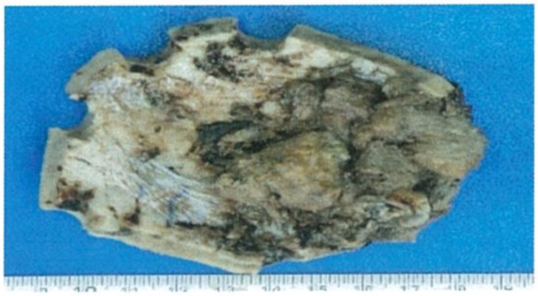


  - Posterior fossa
  - Cerebellar convexity (cerebellopontine angle)
  - Intraspinal: Commonly in the thoracic spinal cord
- Clinical features: Majority are **slow growing**
  - Higher-grade tumors and those with aggressive molecular markers grow rapidly
  - Neurologic deficits depend on tumor location
  - Headache, weakness, and seizures are common (although not specific)
- Imaging: Contrast-enhancing **dural tail sign** at the tumor periphery
  - MRI: Isodense, uniformly with contrast enhancement
  - CT: May show calcifications
  - Peritumoral edema: Commonly seen with secretory, angiomatous, microcystic, lymphoplasmacyte-rich, and high-grade tumors
  - Cyst formation (within or at the periphery)
- Immunohistochemistry:
  - **SSTR2A** (strong and diffuse expression in nearly all subtypes)
  - Progesterone receptor (variable staining, higher-grade tumors may be negative)
  - **EMA** (may be weak, patchy, or absent, especially in fibrous and higher-grade subtypes); vimentin (low specificity), CEA (secretory subtype); H3K27me3 (may be lost in higher-grade subtypes)
- Monosomy 22 and NF2 gene alterations are common
- Proliferation index > 4% have recurrence rates like those of CNS WHO grade 2
- Proliferation index > 20% are associated with mortality rates like those of CNS WHO grade 3 meningiomas
- DNA methylation profiling may be used to separate clinically relevant subgroups of meningioma

Angiomatous meningioma with a reddish, cut surface



Bifrontal lobular meningioma with extension to skull



14. MENINGIOMA

MENINGOTHELIAL MENINGIOMA

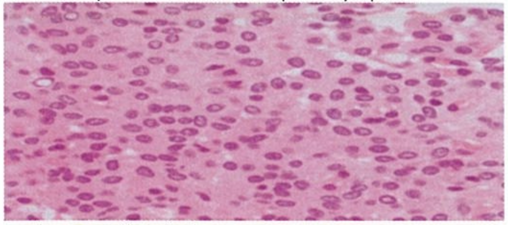
MORPHOLOGY

- Histology: Epithelioid cells form lobules
  - ➢ Monomorphic cells with eosinophilic cytoplasm and indistinct cell borders
  - ➢ Nuclear holes and pseudoinclusions are common
  - ➢ Whorls and psammoma bodies are rare

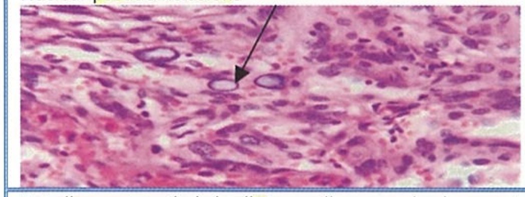
OTHER HIGH YIELD POINTS

- Location: **Skull base**
- Molecular: AKT1 p.E17K mutations, frequently associated with TRAF7, SMO, and PIK3CA mutations
  - ➢ Chromosome 22 deletions are rare
  - ➢ NF2 mutations are rare

Monomorphic cells with eosinophilic cytoplasm



Nuclear pseudoinclusions



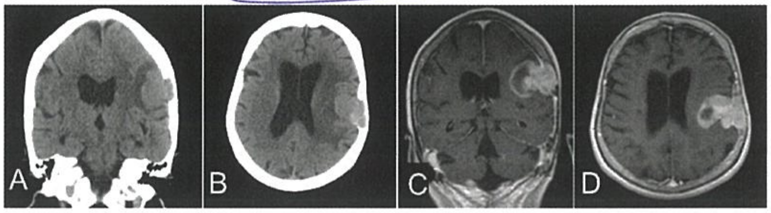
FIBROUS MENINGIOMA

MORPHOLOGY

- Histology: Spindle cells in parallel, storiform, or interlacing bundles in a collagen-rich matrix

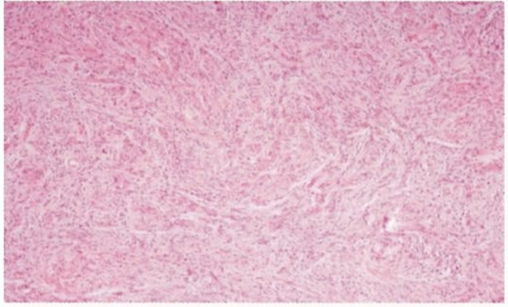
OTHER HIGH YIELD POINTS

- Location: **Convexity**
- IHC: EMA (weak or absent); (+) S100, SSTR2A
- Molecular: 22q deletion (frequent), mutation of retained NF2 allele
- Differential diagnosis: Solitary fibrous tumor (nuclear staining for STAT6)

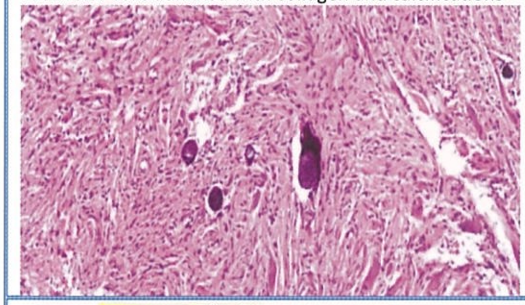


Fibrous meningioma. A. and B. Coronal and axial CT scan showing a frontal, isodense lesion with perilesional edema, bone resorption, and dilation of the ventricular system
C. and D. T1-weighted MRI showing left frontal hyperintense lesion with heterogeneous contrast enhancement, a solid-cystic portion, and dural attachment
Picture courtesy: Felipe Garcia, MD and Julian M. Enriquez, MD

Spindle meningothelial cells in a collagenous background



Fascicular cells admixed with collagen and calcifications



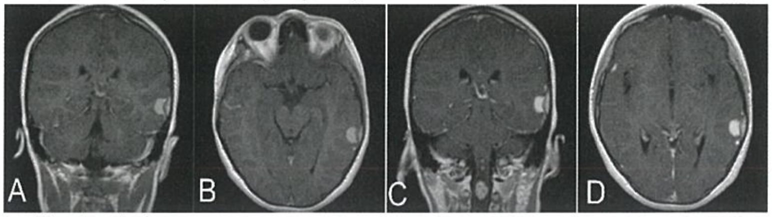
TRANSITIONAL MENINGIOMA

MORPHOLOGY

- Histology: Mixed meningothelial and fibrous patterns
- Whorls and psammoma bodies are common

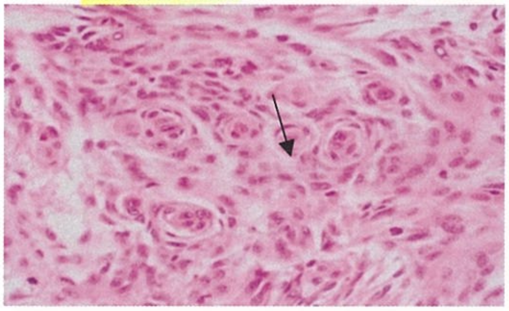
OTHER HIGH YIELD POINTS

- Location: **Convexity**
- Molecular: 22q deletion (frequent), NF2 mutations

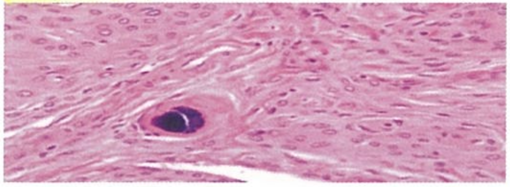


Transitional meningioma
A and B. Coronal T1-weighted MRI showing a small left temporal lesion with homogenous contrast enhancement and dural attachment
C. Coronal T1-weighted MRI showing a cervical lesion with homogenous contrast enhancement in addition to the left temporal lesion
D. Axial section showing a small left temporal lesion with contrast enhancement
Picture courtesy: Felipe Garcia, MD and Julian M. Enriquez, MD

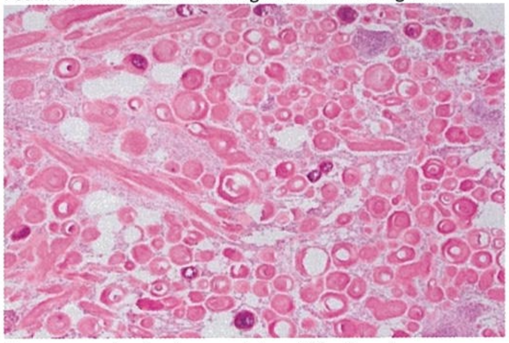
Contains numerous whorls



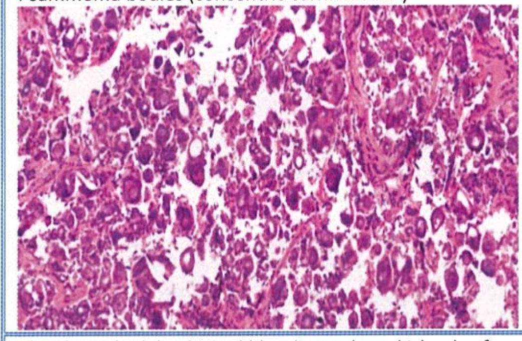
Psammoma body calcification



Psammoma bodies in a background of meningioma



Psammoma bodies (concentric calcifications)



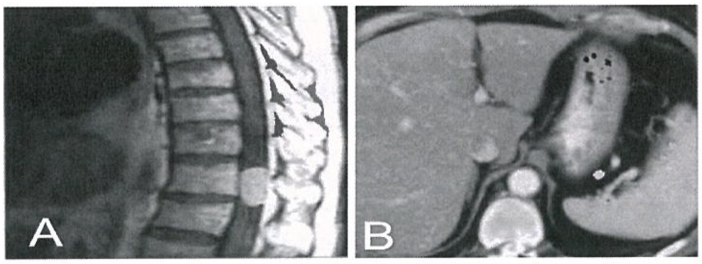
PSAMMOMATOUS MENINGIOMA

MORPHOLOGY

- Histology: Psammoma bodies predominate; meningioma cells are sparse
  - Numerous psammoma bodies can form large, calcified masses
  - Fibrous or transitional subtypes commonly seen in non-calcified foci

OTHER HIGH YIELD POINTS

- Location: **Thoracic spine (middle-aged to elderly women)**
- Molecular: 22q deletions, NF2 mutations



Meningioma T8-T9, 76-year-old female. A. Sagittal T1-weighted MRI showing homogeneous enhancement with gadolinium

B. Axial T1-weighted MRI showing an intradural, extramedullary lesion

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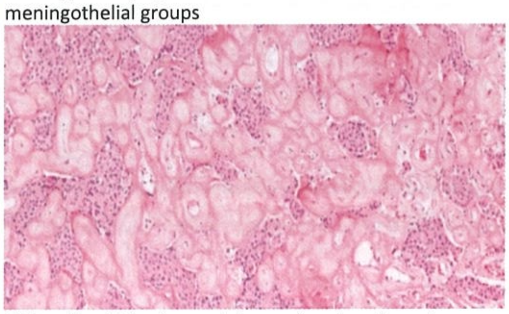
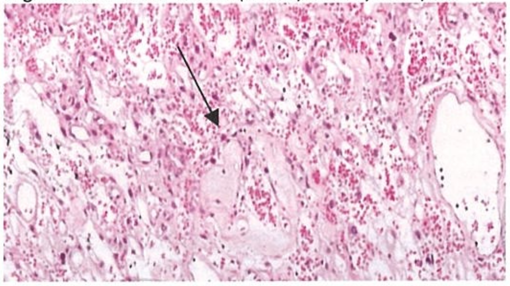
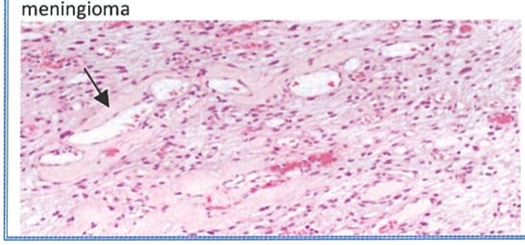
Closely packed, hyalinized blood vessels and islands of meningothelial groups



High ratio of blood vessels (arrow) and erythrocytes



Hyalinized blood vessels (arrow) in a background of meningioma



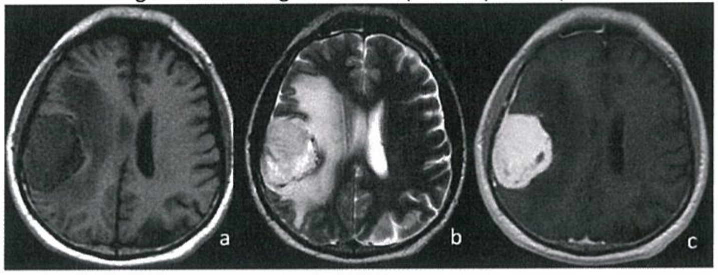
ANGIOMATOUS MENINGIOMA

MORPHOLOGY

- Histology: Predominantly hyalinized small blood vessels in a background of meningioma cells
  - Blood vessels may be thin- or thick-walled and variably hyalinized
  - Microcystic and metaplastic subtypes often seen with degenerative nuclear atypia

OTHER HIGH YIELD POINTS

- Imaging: Peritumoral edema
- Molecular: Chromosome 5 gain
- Differential diagnosis: Hemangioblastoma (inhibin positive)

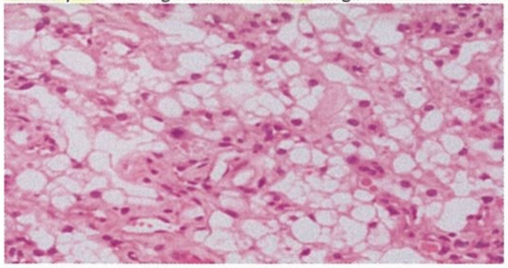


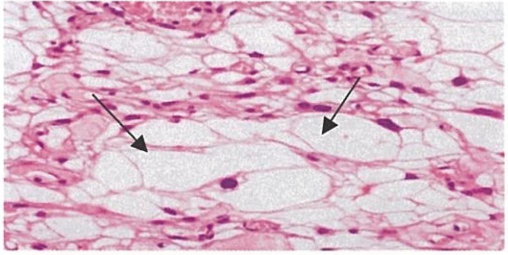
Angiomatous meningioma in a 59-year-old male with progressive right-sided hypoesthesia and generalized tonic-clonic seizures. MRI shows extra-axial, 5 cm heterogenous tumor on the right parietal lobe with discrete hyperintensity on T1 and T2 as well as a marked perilesional hyperintensity (edema)

Picture courtesy: Julian M. Enriquez, MD

Path Presenter   Path Presenter

14. MENINGIOMA


Microcysts forming a cobweb-like background


Thin processes and nuclear atypia
Picture courtesy: Takashi Fujisawa, MD, PhD

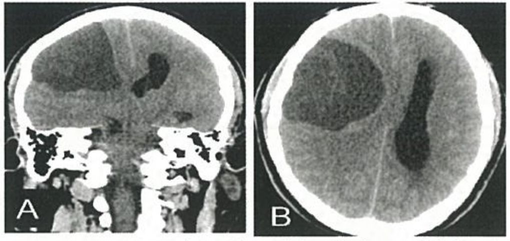
MICROCYSTIC MENINGIOMA

MORPHOLOGY

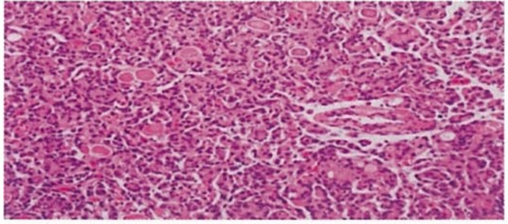
- Histology: Microcysts formed by cells with thin, elongated processes, creating a cobweb-like background
  - ➢ Degenerative nuclear atypia

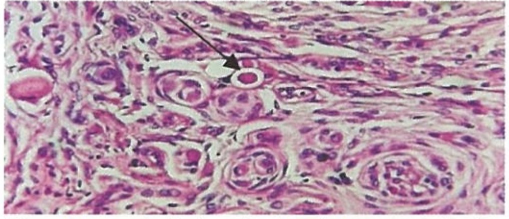
OTHER HIGH YIELD POINTS

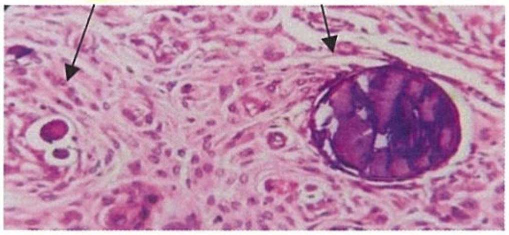
- Imaging: Peritumoral edema
- Molecular: Chromosome 5 gain



Microcystic meningioma in a 55-year-old male with headaches and left pelvic limb paresis.
A. Coronal CT scan showing an isodense right frontal lesion near the convexity with a large cystic portion that compresses the right frontal ventricular horn
B. Axial CT scan showing a right frontal lesion with a solid-cystic component that obliterates the right ventricular horn


Pseudopsammoma bodies in gland-like spaces


Meningothelial whorls mixed with secretory globules


A true psammoma body and a pseudopsammoma body

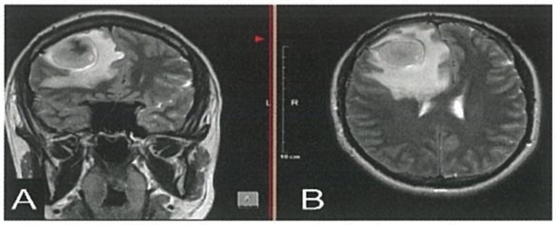
SECRETORY MENINGIOMA

MORPHOLOGY

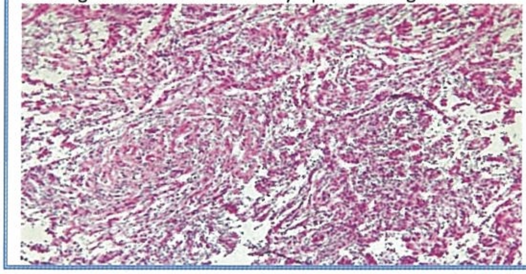
- Histology: Pseudopsammoma bodies in gland-like epithelial spaces
  - ➢ PAS-positive eosinophilic secretions (pseudopsammoma bodies)

OTHER HIGH YIELD POINTS

- Imaging: Peritumoral edema
- IHC: (+) CEA and cytokeratins (pseudopsammoma bodies and surrounding cells)
- Molecular: Combined KLF4 p.K409Q and TRAF7 mutations, isolated KLF4 mutations



Secretory meningioma. A. Coronal T2-weighted MRI showing a heterogeneous right frontal lesion with vasogenic, perilesional edema compressing the right ventricular frontal horn
B. Axial T2-weighted MRI showing a frontal meningioma with dural attachment and prominent adjacent vasogenic edema that extends and compresses the ventricular system


Meningothelial whorls with a lymphoid background

LYMPHOPLASMACYTE-RICH MENINGIOMA

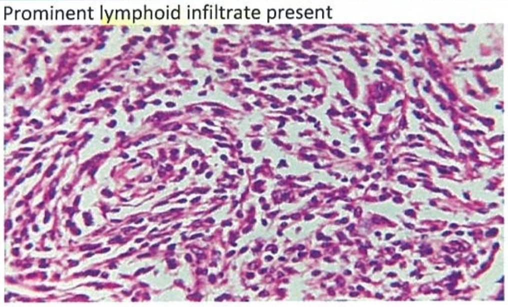
MORPHOLOGY

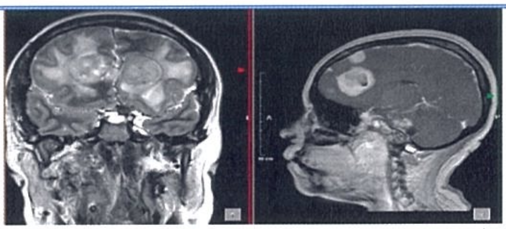
- Histology: Extensive chronic inflammatory infiltrates predominate over the meningothelial component
  - ➢ Macrophages predominate; plasma cells are sparse

OTHER HIGH YIELD POINTS

- Differential diagnosis: Inflammatory disorders with patchy meningothelial hyperplasia

Prominent lymphoid infiltrate present

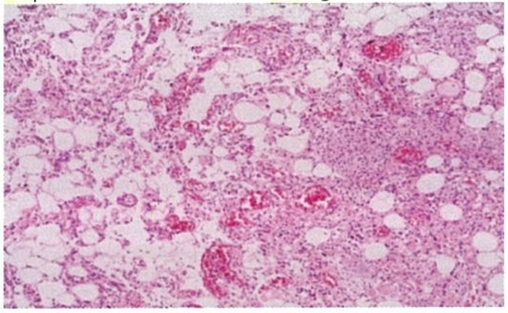




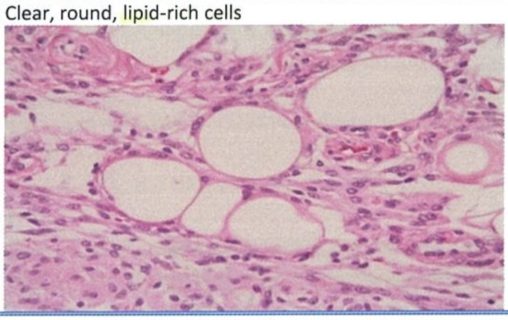
Lymphoplasmacyte-rich meningioma in a 33-year-old female. A. Coronal T2-weighted MRI showing a bifrontal, isointense, heterogeneous falcine lesion producing brain edema B. Sagittal T1-weighted MRI of the same patient showing the previous contrast-enhancing lesion as well as a 2nd lesion with the same characteristics in the frontal dura

Picture courtesy: Paulo M Tabera, MD

Adipose cells intermixed with meningothelial cells



Clear, round, lipid-rich cells



METAPLASTIC MENINGIOMA

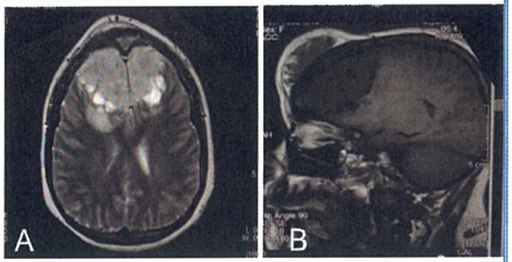
Path Presenter

MORPHOLOGY

- Histology: Mesenchymal components (osseous, cartilaginous, lipomatous, myxoid, and xanthomatous tissue) and extensive chronic inflammatory infiltrates predominate over the meningothelial component
  - ➢ The mesenchymal component is variable

OTHER HIGH YIELD POINTS

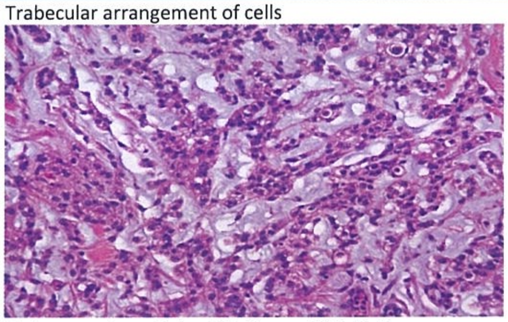
- Molecular: Chromosome 5 gain



Metaplastic meningioma in a 46-year-old female with headaches. A. Axial T2-weighted MRI with a bifrontal, heterogeneous, hyperintense lesion that compresses both frontal lobes with peripheral cystic lesions and perilesional edema. An extracranial hyperintense lesion can be seen above the frontal bone B. Sagittal T1-weighted MRI of the same lesion showing destruction of the skull in its frontal portion with significant compression of the frontal lobes

Picture courtesy: Paulo M. Tabera, MD

Trabecular arrangement of cells



Picture courtesy: Takashi Fujisawa, MD, PhD

CHORDOID MENINGIOMA (CNS WHO GRADE 2)

MORPHOLOGY

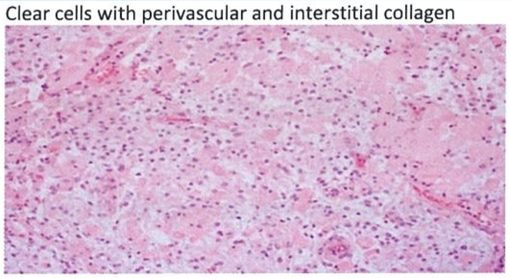
- ➢ Histology: Cords or trabeculae of small, epithelioid, vacuolated cells in a mucin-rich matrix, often admixed with typical meningioma

OTHER HIGH YIELD POINTS

- Molecular: Chromosome 2p deletions
- Often large, supratentorial tumors
- CNS WHO grade 2 tumor

Path Presenter

Clear cells with perivascular and interstitial collagen



Monomorphous cells with clear vacuolated cytoplasm

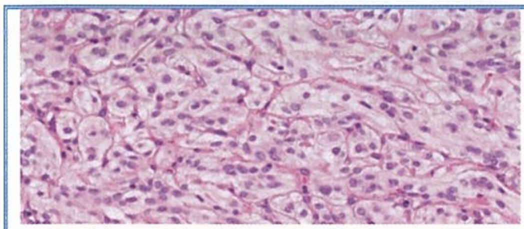
CLEAR CELL MENINGIOMA (CNS WHO GRADE 2)

MORPHOLOGY

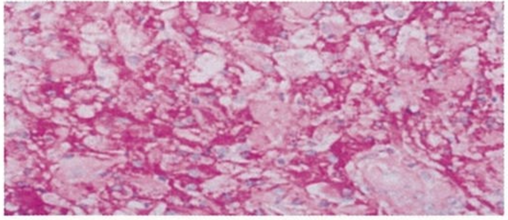
- Histology: Round to polygonal cells with clear, glycogen-rich cytoplasm and prominent perivascular and interstitial collagen
  - ➢ Patternless or sheeting architecture
  - ➢ The collagen occasionally coalesces into large, acellular zones of collagen
  - ➢ PAS-positive and diastase-sensitive cytoplasm
  - ➢ Whorl formation is subtle, and psammoma bodies are inconspicuous

OTHER HIGH YIELD POINTS

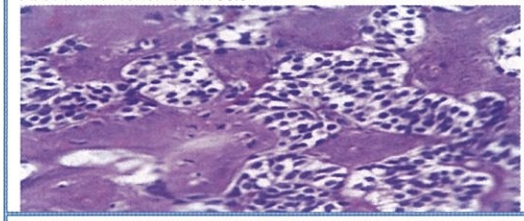
- IHC: Loss of nuclear expression of SMARCE1
- Molecular: SMARCE1 mutations (somatic and germline)



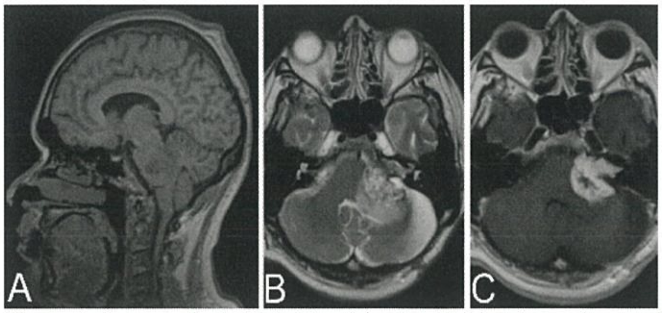
PAS-positive cytoplasm in tumor cells



Areas of extensive fibrosis

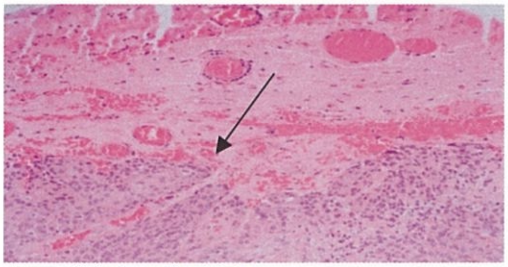


- Location: Common in **cerebellopontine angle** and spine (cauda equina)
- Common in younger patients
- Cerebrospinal fluid seeding
- CNS WHO grade 2 tumor

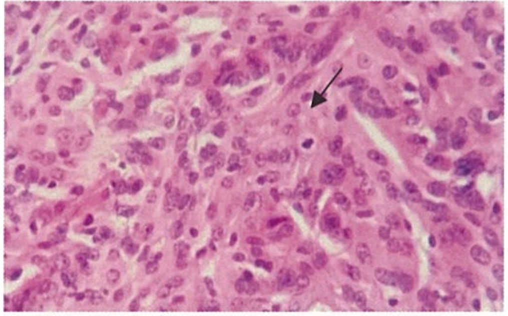


Clear cell meningioma. A. Sagittal T1-weighted MRI showing a heterogeneous, hypointense lesion with a clear CSF cleft sign indicating an extra-axial lesion within the pons B. Axial T2-weighted image showing the same lesion which is heterogeneous in comparison to the brainstem parenchyma which produces a significant compression of the left cerebellar peduncles C. Axial T1-weighted image showing a contrast-enhancing lesion that appears to grow from the inner auditory meatus with regular borders and an hypointense inner portion. No significant edema is seen in the adjacent tissue
Picture courtesy: Paulo M. Tabera, MD

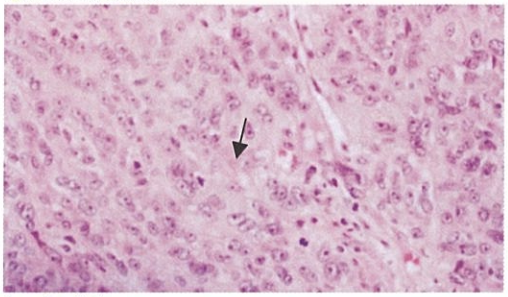
Brain invasion



Hypercellularity and mitosis



Prominent nucleoli



Small cell change

ATYPICAL MENINGIOMA (CNS WHO GRADE 2)

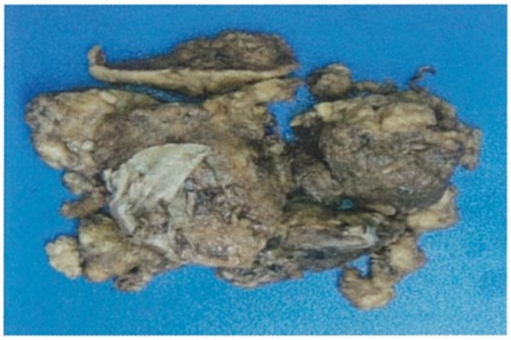
MORPHOLOGY

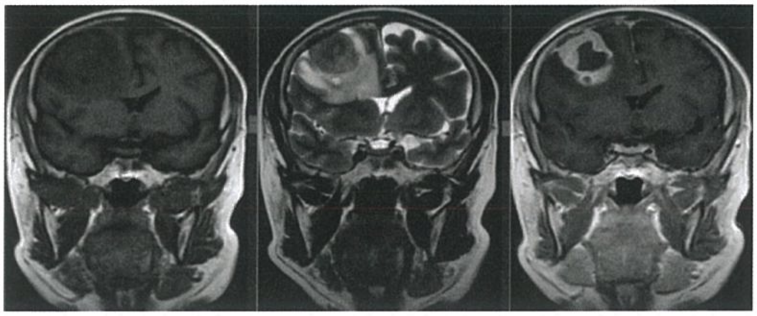
- Histology: Any histologic subtype characterized by increased mitotic activity (4-19 mitoses/1) HPF

  OR
- Brain invasion

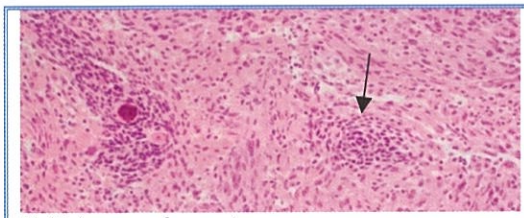
  OR
- **At least 3 of the following:**
  - Small cells with high N:C ratio
  - Prominent nucleoli
  - Sheeting (sheet-like or uninterrupted, patternless growth)
  - Foci of spontaneous (non-iatrogenic) necrosis

Atypical meningioma: Irregular, lobulated, grayish-yellow tumor

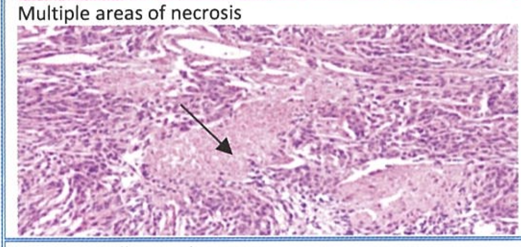




Atypical meningioma. A. Coronal T1-weighted MRI showing a hypointense lesion compressing the right frontal lobe



Multiple areas of necrosis

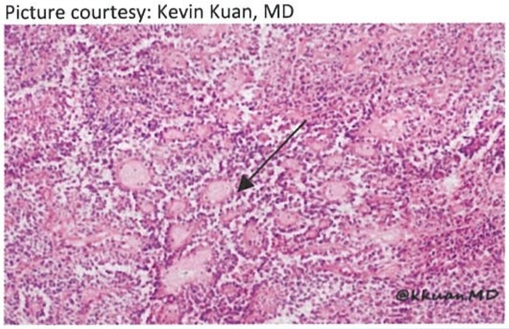


B. Coronal T2-weighted MRI showing the same hypointense lesion with significant perilesional edema of the ipsilateral frontal lobe producing a mild midline displacement C. Coronal T1-weighted image showing a contrast-enhancing lesion with a clear dural tail sign. The center of the lesion appears hypointense, indicating necrosis which is characteristic of this type of meningioma

Picture courtesy: Paulo M. Tabera, MD

Path Presenter

Pseudopapillary architecture
Picture courtesy: Kevin Kuan, MD



PAPILLARY MENINGIOMA (CNS WHO GRADE 3)

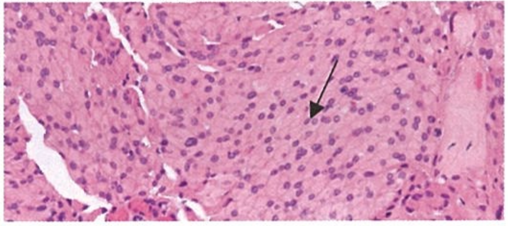
MORPHOLOGY

- Histology: Perivascular pseudopapillary pattern
  - ➢ Tumor cells arranged around thin-walled blood vessels (perivascular, pseudorosette-like pattern)
  - ➢ Occasional rhabdoid cytomorphology

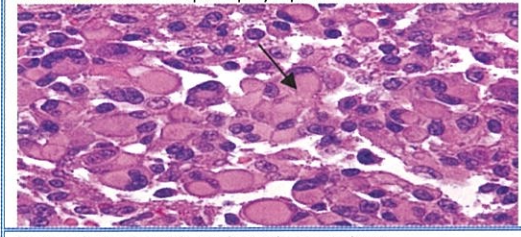
OTHER HIGH YIELD POINTS

- Imaging: Peritumoral edema, bone hyperostosis or destruction or cyst formation
- Molecular: PNRM1 commonly mutated or deleted, BAP1 mutations
- Focal papillary architecture without any other higher-grade features does not qualify for CNS WHO grade 2 or 3 designations

Proliferation of solid sheets with eosinophilic cells



Rhabdoid cells with plump cytoplasm and eccentric nuclei



RHABDOID MENINGIOMA (CNS WHO GRADE 3)

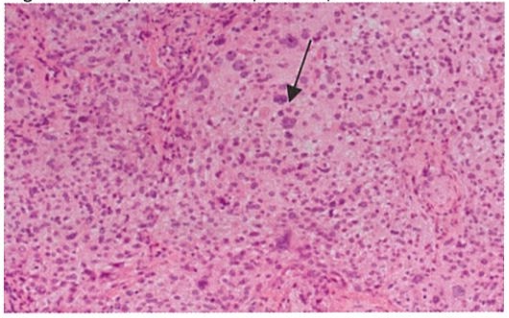
MORPHOLOGY

- Histology: Characterized by rhabdoid cells with eccentric nuclei, open chromatin, macronucleoli, and eosinophilic perinuclear inclusions (whorled fibrils or compact and waxy spheres)
  - ➢ Typically increased mitotic activity

OTHER HIGH YIELD POINTS

- IHC: Loss of BAP1 expression (associated with aggressive behavior and corresponds to CNS WHO grade 3)
- Molecular: Subset have germline BAP1 mutation
- Graded similarly to non-rhabdoid meningioma; focal rhabdoid features without any other higher-grade features does not qualify for CNS WHO grade 2 or 3 designations
- Overlap between histologic and genetic features of rhabdoid and papillary meningiomas

High cellularity with nuclear pleomorphism



ANAPLASTIC (MALIGNANT) MENINGIOMA (CNS WHO GRADE 3)

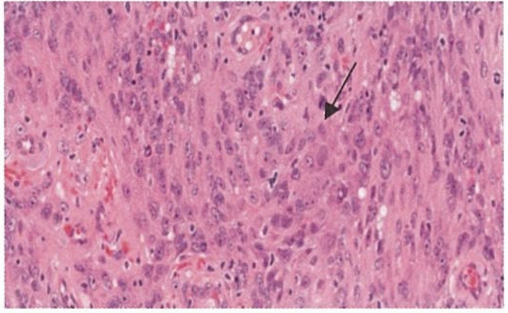
MORPHOLOGY

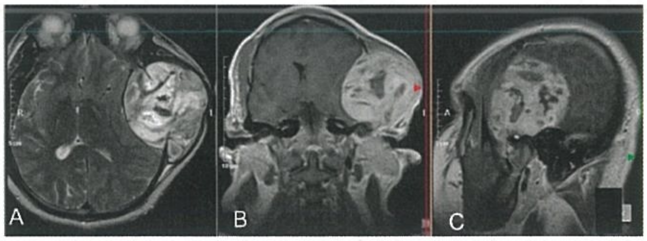
- High-grade meningioma with malignant cytomorphology (anaplasia) that can resemble carcinoma, high-grade sarcoma, or melanoma OR has increased mitotic activity (≥ 20 mitoses/10 HPF) OR harbors a TERT promoter mutation OR homozygous CDKN2A and/or CDKN2B deletion

OTHER HIGH YIELD POINTS

- Loss of H3 p.K28me3 is associated with shorter overall survival

Multiple mitoses



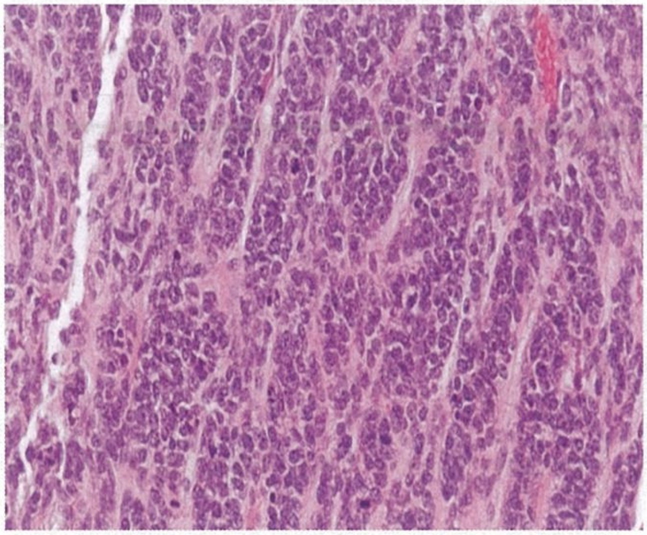


Anaplastic meningioma.

A. Axial T2-weighted MRI showing a hyperintense lesion with intra- and extracranial portions. This lesion compresses the left frontal and temporal lobes

B. Coronal T1-weighted MRI showing the same lesion with significant contrast enhancement

C. Sagittal T1-weighted MRI showing the same contrast-enhancing lesion with a loss of signal indicating the presence of large-caliber vessels vascularizing the tumor



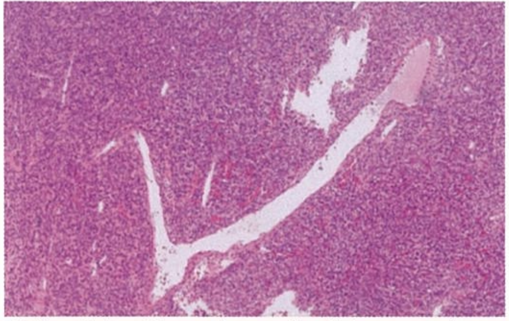
MESENCHYMAL TUMORS

EMILIE RUSSLER-GERMAIN, MD, PhD
RAQUEL T. YOKODA, MD

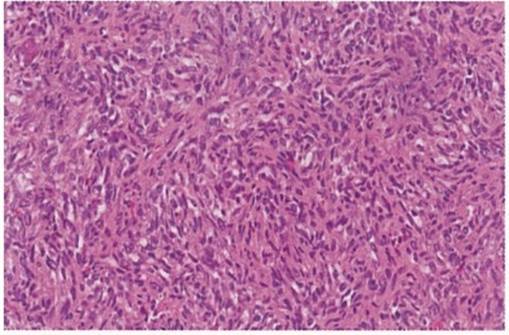
15. MESENCHYMAL TUMORS

CNS MESENCHYMAL TUMORS

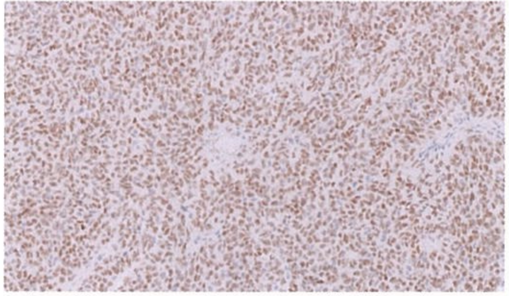
Dilated staghorn vessels



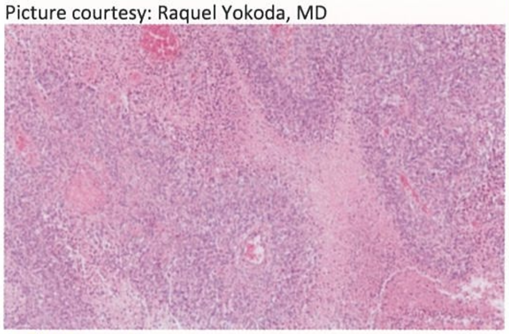
Highly cellular with round to ovoid cells in a patternless pattern



STAT6 positive, diffuse nuclear stain



Solitary fibrous tumor (CNS WHO grade 3) showing necrotic areas and increased mitotic activity
Picture courtesy: Raquel Yokoda, MD



Path Presenter

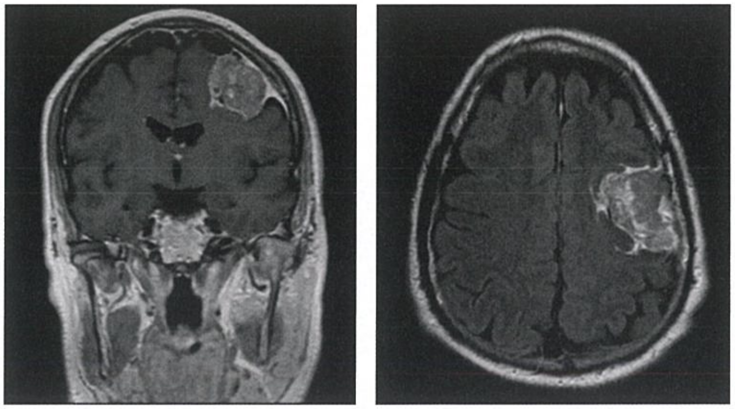
SOLITARY FIBROUS TUMOR

MORPHOLOGY

- Gross: White to brown, firm, rubbery
- Smear: Fine, linear, fibrillary cytoplasm
- Spindled to ovoid, bland, monomorphic cells
- Classic solitary fibrous tumor (SFT) morphology
  - Spindled cells in bands separated by dense collagen (keloidal type)
  - Dilated vessels with thick, sclerotic walls
- No calcifications present
- Grading:
  - Grade 1: < 5 mitoses/10 HPF
  - Grade 2: ≥ 5 mitoses/10 HPF, no necrosis
  - Grade 3: ≥ 5 mitoses/10 HPF, with necrosis

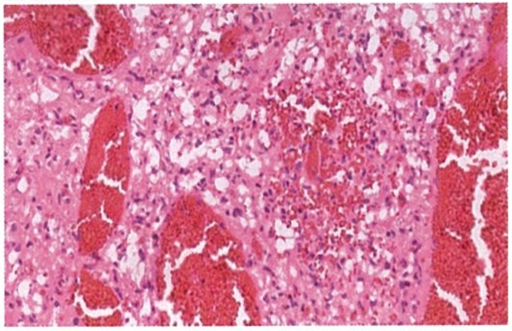
OTHER HIGH YIELD POINTS

- Clinical:
  - Mean age ~50 years, rare occurrences in pediatric population
  - Mostly **supratentorial** (skull base, parasagittal, falcine, 10% spinal)
  - **Dural based**
  - High rate of recurrence/metastasis in the CNS
- Immunohistochemistry:
  - **STAT6 positive, nuclear**
  - **CD34 positive**
- NAB2::STAT6 fusion (inv12(q13q13))
- TERT promoter mutations in 10-30% meningeal SFTs
- The term "hemangiopericytoma" is no longer recommended as synonymous by the CNS 5 WHO
  - Tumors with SFT-like morphology but negative for STAT6 are still called "hemangiopericytoma" (but only in head and neck)
- Radiology:
  - T1 isointense
  - T2 heterogeneous/high intensity
  - Heterogeneous contrast enhancement with a **dural tail**
  - Circumscribed but irregular contours
  - **Cannot be distinguished from meningioma**

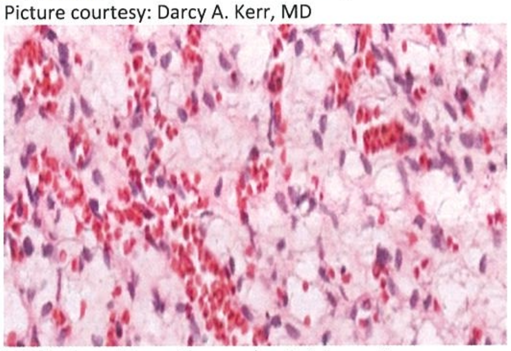


T1-weighted, post-contrast coronal and axial images

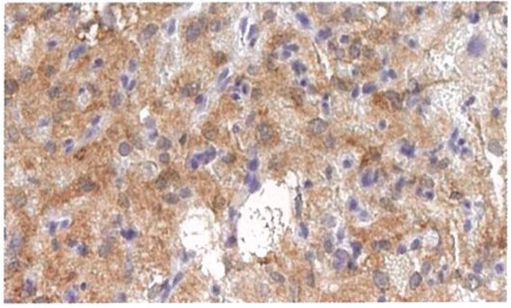
Highly vascular with a range of vessel sizes; vacuolated tumor cells



Vacuolated tumor cells with intervening vessels
Picture courtesy: Darcy A. Kerr, MD



Inhibin A positive with granular staining pattern
Picture courtesy: Darcy A. Kerr, MD



Path Presenter

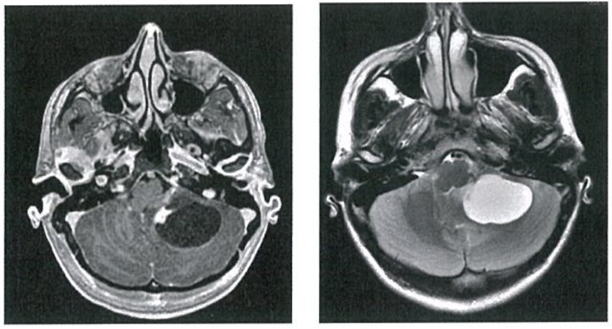
HEMANGIOBLASTOMA (CNS WHO GRADE 1)

MORPHOLOGY

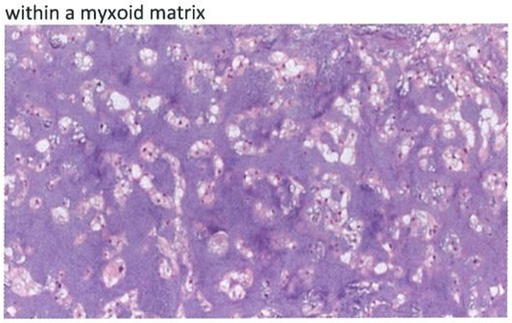
- Gross: Solid and cystic with mural nodules, well circumscribed, yellow, possibly hemorrhagic
- Smears poorly (no single cells), spindled cells with cytoplasmic vacuoles
- Highly vascular with a range of vessel sizes
- Tumor cells with lipid-rich cytoplasmic vacuoles and variable nuclear atypia
- **Sharp border with normal tissue**
- Mitoses rare/absent
- Possible dense sclerosis, hyaline globules, and extramedullary hematopoiesis
  - Reticular = high vasculature to tumor ratio
  - Cellular = low vasculature to tumor ratio with nested appearance
- **Can be identical to metastatic clear cell renal cell carcinoma**
- Surrounding parenchyma with astrocytic gliosis and Rosenthal fibers

OTHER HIGH YIELD POINTS

- Clinical:
  - Can occur with **VHL syndrome** (sometimes with multiple tumors) or can be sporadic
  - Mostly **infratentorial (cerebellum)/spinal**, retinal
  - May produce erythropoietin, causing polycythemia
- Frozen: Positive for oil red O
- Immunohistochemistry:
  - **(+) Inhibin A** (granular, variable), GLUT1 (diffuse, weak), S100 (diffuse, strong), CAIX, NSE
  - Vessel endothelial cells positive for CD31, CD34, FXIIIa, and ERG
  - (-) EMA, PAX8, CAM 5.2, CD10, Ki-67 low
- VHL germline mutations (10%, chromosome 3p25), VHL somatic mutations, activating EPAS1 (HIF2A) mutations
- Radiology: Discrete, enhancing, and cystic with avidly enhancing nodules



Conventional chordoma. Tumor cells in cohesive cords within a myxoid matrix

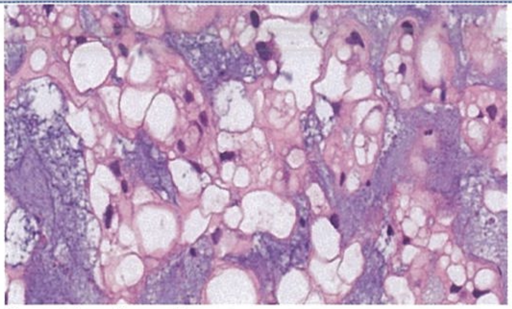


Physaliphorous cells

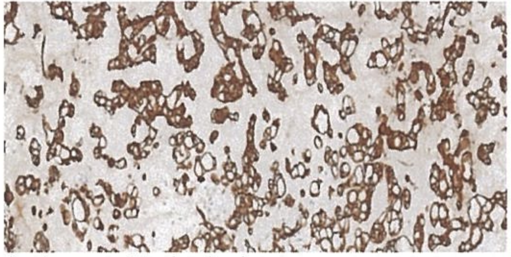
CHORDOMA

MORPHOLOGY

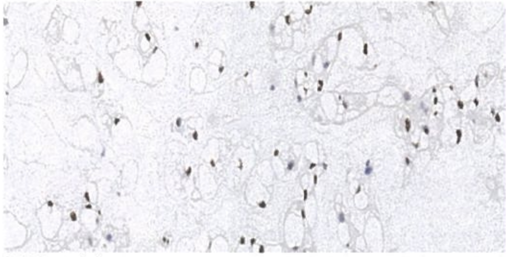
- Gross: Solid, lobulated, well circumscribed, soft/gelatinous
- Smear: Cellular with myxoid matrix, cells with eosinophilic cytoplasm
- **Conventional:**
  - Lobulated with fibrous septae
  - Myxoid matrix
  - Tumor cells in cohesive cords/small groups with clear to eosinophilic cytoplasm, epithelioid to vacuolated (multi-vacuolated = physaliphorous cells), variable nuclei (bland to atypical)
  - Mitoses scarce/absent
  - Chondroid chordoma: Areas resembling hyaline cartilage
- **Poorly differentiated:**
  - Solid, cellular, epithelioid, and sometimes rhabdoid
  - Mitoses present
  - No myxoid matrix



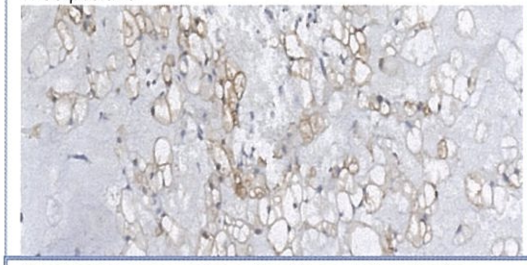
Pancytokeratin positive



Brachyury positive (nuclear)



S100 positive



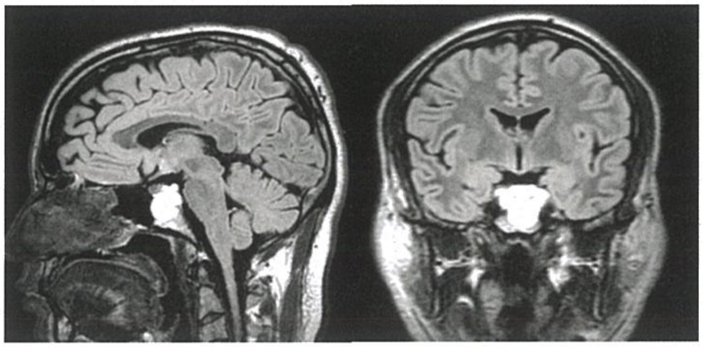
  - Necrosis
  - Retained brachyury expression, loss of SMARCB1 (INI1)
- **Dedifferentiated:**
  - Appearance of pleomorphic spindle cell sarcoma adjacent to conventional chordoma
  - Loss of brachyury expression in dedifferentiated components

OTHER HIGH YIELD POINTS

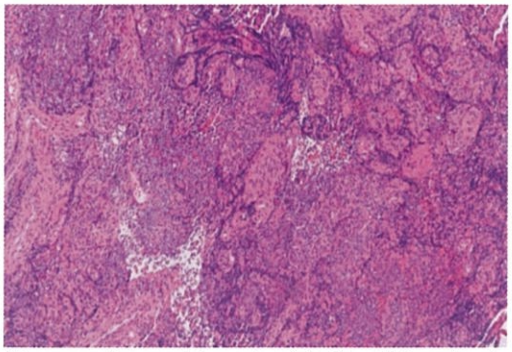
Path Presenter

- Clinical:
  - 4th-8th decade, young children with **tuberous sclerosis**
  - Poorly differentiated forms more common in children
  - Rare cases with germline TBXT mutation
  - Axial skeleton (esp. **clivus/sacrococcygeal area**)
  - Derived from the **notochord**
- Radiology:
  - Lytic bone lesions extending into soft tissue
  - Contrast enhancement
  - Hypointense on T1
  - Hyperintense on T2
- Immunohistochemistry:
  - (+) EMA, keratin, S100, brachyury (nuclear)
  - Poorly differentiated: Loss of SMARCB1 (INI1)
- Molecular: FISH for SMARCB1 deletion in poorly differentiated

MRI FLAIR Sagittal View MRI FLAIR Coronal View



Sheets of monomorphic cells with vague lobularity



Monomorphic, round to oval nuclei with a high nuclear to cytoplasmic ratio and clear cytoplasm

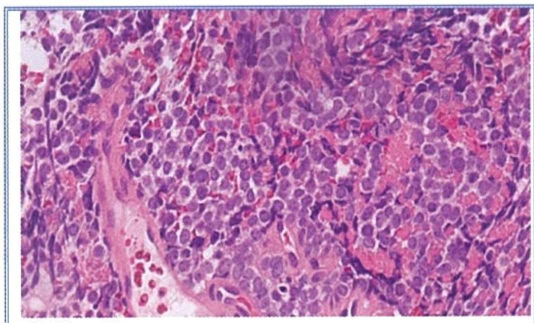
EWING SARCOMA

MORPHOLOGY

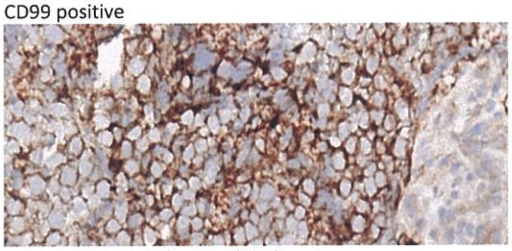
- Gross: Gray fleshy mass with poorly defined borders, necrosis, and hemorrhage
- Smear: Cellular, loose groups, high N:C ratio
- Monomorphic, round to oval nuclei with fine chromatin and clear cytoplasm (cytoplasmic glycogen)
- High cellularity with frequent coagulative necrosis
- Sheets with vague lobular architecture
- Mitoses frequent
- Coagulative necrosis and hemorrhage
- Rare subset with Homer Wright-type rosettes (neuronal differentiation)
- Vascular, with congestion

OTHER HIGH YIELD POINTS

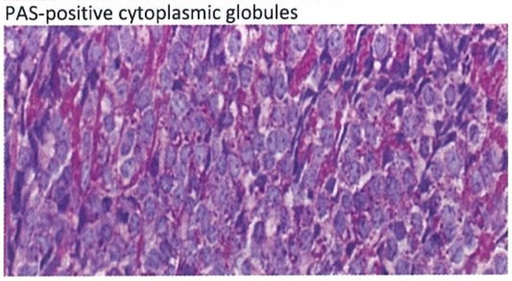
- Clinical:
  - **Children and young adults**
  - CNS involvement: Most commonly direct extension from epidural space and **bone**, metastasis



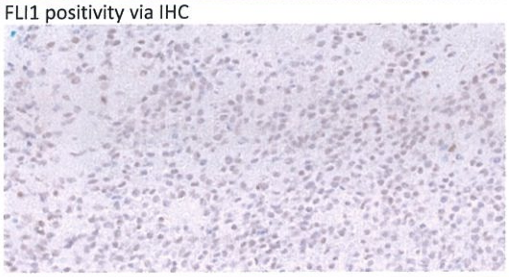
CD99 positive



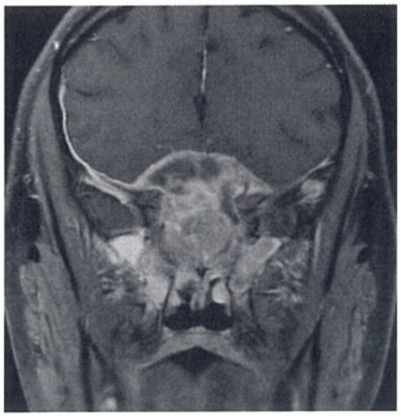
PAS-positive cytoplasmic globules



FLI1 positivity via IHC



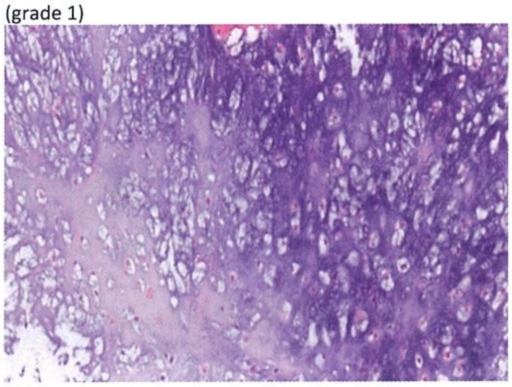
  - Primary CNS: Cauda equina/filum terminale, dura, peripheral nerve, intraparenchymal
- Radiology:
  - Enhancing mass
  - Dural tail may mimic meningioma
  - **Bone destruction**
- Immunohistochemistry:
  - **(+) CD99 (membranous), NKX2.2, FLI1 (nuclear)**
  - Synaptophysin/chromogranin variably positive
  - Cytokeratin positive in rare cases
- PAS positive (cytoplasmic glycogen, diastase sensitive)
- **EWSR1** fusion with **ETS family** fusion partners:
  - **FLI1** (most common, 85%), t(11;22)(q24;q12)
  - ERG t(21;22)
  - ETV1, ETV4, FEV
- Rare cases without EWSR1 rearrangements have **FUS** rearrangements



Brain MRI T1 Post contrast image (Coronal view) showing an enhancing Ewing sarcoma

Path Presenter

Blue-gray cartilage matrix with increased cellularity (grade 1)



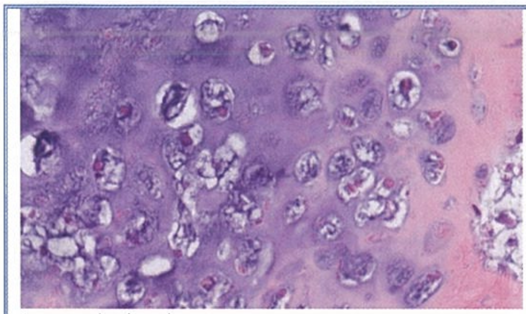
Mild nuclear atypia, absent mitoses (grade 1)

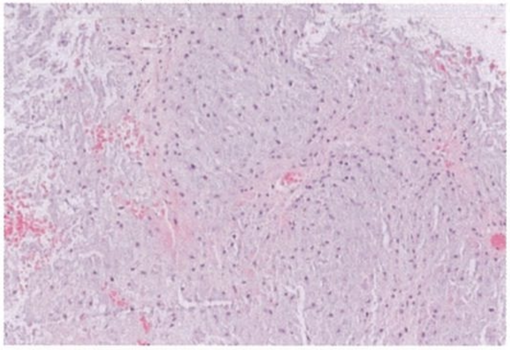
CHONDROSARCOMA

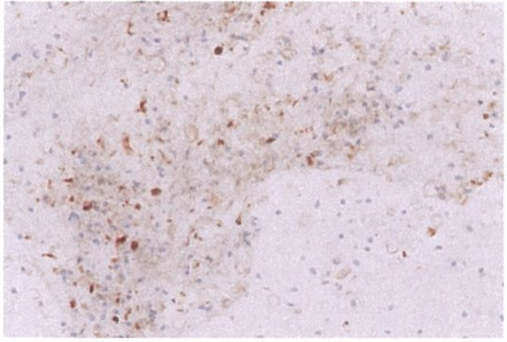
Path Presenter

MORPHOLOGY

- Gross:
  - **Blue-gray, glistening surface**
  - Cystic, calcified, and hemorrhagic areas possible
  - Mesenchymal and high-grade types show necrosis
- Chondrosarcoma, grade 1
  - **Blue-gray cartilage matrix with large chondrocytes**
  - Mildly increased cellularity with hyperchromatic, atypical nuclei with some binucleation; absent mitoses
- Chondrosarcoma, grade 2
  - Increased cellularity, increased nuclear atypia, rare mitoses
  - Myxoid changes
- Chondrosarcoma, grade 3
  - Marked nuclear pleomorphism, spindle cells, frequent mitoses
  - Myxoid changes
- Dedifferentiated:
  - Rare as CNS primary
  - Low- and high-grade components with an abrupt transition


Low-grade chondrosarcoma
Picture courtesy: Raquel Yokoda, MD

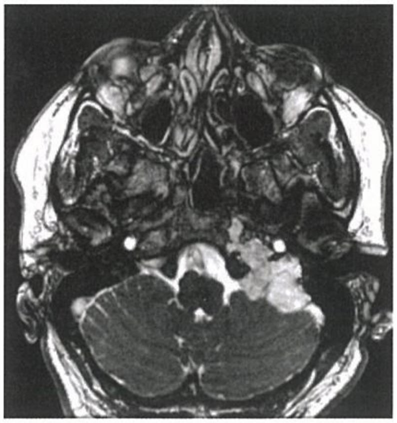

D2-40 stain
Picture courtesy: Raquel Yokoda, MD



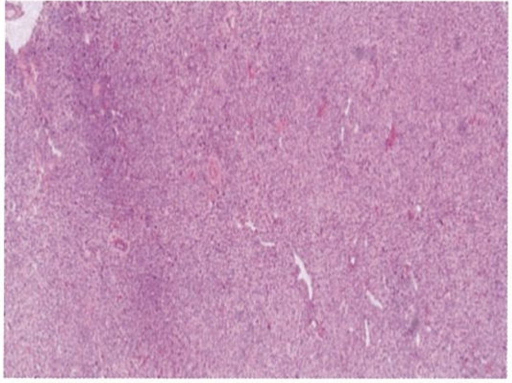
- **Mesenchymal chondrosarcoma:**
  - **Biphasic**, with **small cells with scant cytoplasm,** interspersed with areas of benign-appearing hyaline cartilage

OTHER HIGH YIELD POINTS

- Clinical:
  - **Sporadic**
  - Wide age range (mesenchymal chondrosarcoma 10-30 years old)
  - Increased incidence in conditions causing enchondromatosis (Ollier disease and Maffucci syndrome) and with germline EXT1 or EXT2 mutations
  - **Skull base** (most common), spine, and sacrum
  - Parafalcine is less common (low grade, good prognosis, younger patients)
  - Mesenchymal chondrosarcoma is often dural based
  - Metastasis from peripheral sites is possible
- Immunohistochemistry:
  - **(+) S100, vimentin, D2-40** (chondroid marker)
  - Mesenchymal chondrosarcoma positive for CD99 and SOX9
  - IDH1 R123H mutation present (< 20% of IDH mutations)
- **IDH1 and IDH2 mutations in ~60%**
- Mesenchymal chondrosarcoma: **HEY1::NCOA2 fusion**
- Radiology:
  - Soft tissue extension variable
  - Calcification possible
  - Parafalcine location mimics meningioma
  - Hypointense on T1
  - Contrast enhancement variable


MRI axial 3D showing a low-grade chondrosarcoma arising from the jugular foramen

Sheets of cells with hemangiopericytoma-like vessels


Pleomorphic nuclei with eosinophilic, intracytoplasmic hyaline globules

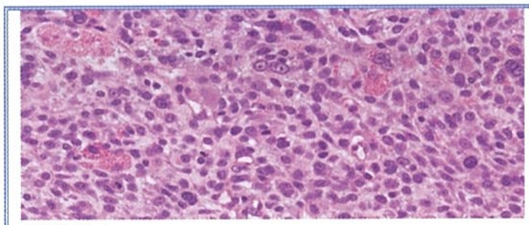
PRIMARY INTRACRANIAL SARCOMA, DICER1-MUTANT

MORPHOLOGY

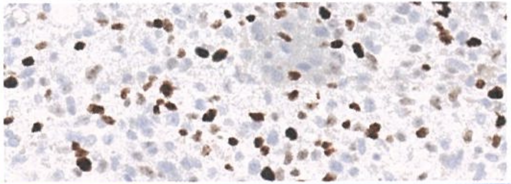
- **Variable morphology: Monomorphic spindle cells in patternless/fascicular patterns** vs. **pleomorphic nuclei in patternless patterns**
- **Brisk mitoses with atypical figures**
- **Eosinophilic, intracytoplasmic hyaline globules**
- Necrosis
- Hemangiopericytoma-like vessels
- Scarce rhabdomyoblasts are detectable in some studies
- Cartilaginous differentiation is possible

OTHER HIGH YIELD POINTS

- Occurs in pediatric population; increased in patients **with DICER1 syndrome** and **neurofibromatosis type 1**
- Supratentorial with leptomeningeal involvement
- Radiology: Solid and cystic with intratumoral bleeding, heterogeneous contrast enhancement, associated with meninges
- Immunohistochemistry:
  - **SMA, desmin, and myogenin are variably positive**
  - **Ki-67 staining > 50%**



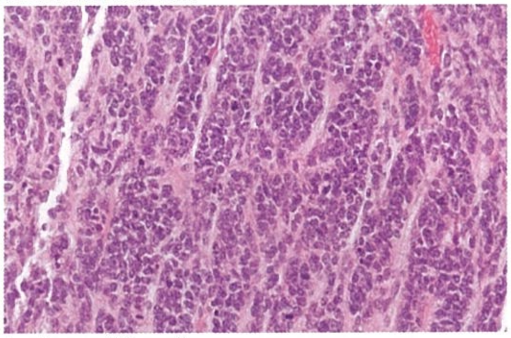
Ki-67 high



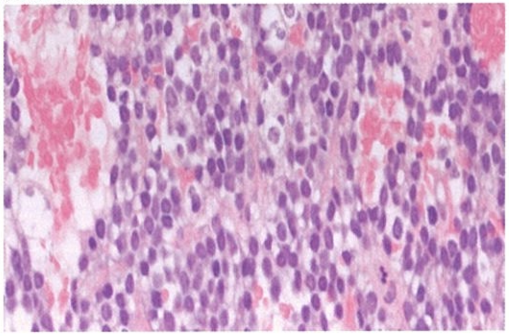
  - ➢ p53-mutant staining pattern in a subset
  - ➢ ATRX loss of nuclear staining in a subset
  - ➢ H3K27me3 loss, patchy to complete
- Reticulin stain: Abundant intercellular basement membrane
- **Eosinophilic globules stain with PAS-D and alpha-1 antitrypsin**
- **DICER1 mutation** (chromosome 14q32), also high frequency of TP53, ATRX, NF1, other RAS pathway mutations

Path Presenter

Small round blue cells



Small round blue cells



CIC-REARRANGED SARCOMA

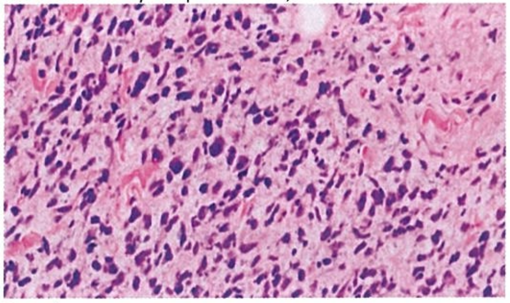
MORPHOLOGY

- Gross: White/tan, well circumscribed, soft, with hemorrhage and necrosis
- **Morphologic features of Ewing sarcoma** (see above), **more heterogeneity:**
  - ➢ Sheets of small round cells with vague lobular architecture and necrosis
  - ➢ Focal spindle, epithelioid, and rhabdoid differentiation
  - ➢ Prominent nucleoli and eosinophilic cytoplasm amongst myxoid stroma

OTHER HIGH YIELD POINTS

- Clinical: Primarily adolescents and young adults
  - ➢ Extra-osseous
  - ➢ Intra-axial and extra-axial
  - ➢ Primary or CNS metastases from peripheral sites
  - ➢ Aggressive
- Radiology: Cystic or solid-enhancing mass
- **CIC** fusion with various gene partners
  - ➢ **NUTM1, most common in primary CNS**
  - ➢ DUX4 fusion, most common in peripheral tumors (t(4;19)(q35;q13) or t(10;19)(q26;q13))
  - ➢ Other uncommon fusion partners are FOXO4, LEUTX, and NUTM2A
- Immunohistochemistry:
  - ➢ **CD99 patchy**
  - ➢ NKX2.2 negative
  - ➢ (+) WT, ETV4
  - ➢ **CIC::NUTM1 fusions are NUT positive**
  - ➢ SMARCB1 and SMARCA4 retained

Embryonal rhabdomyosarcoma
Picture courtesy: Raquel Yokoda, MD



Desmin

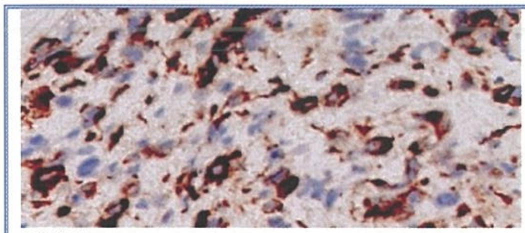
RHABDOMYOSARCOMA

MORPHOLOGY

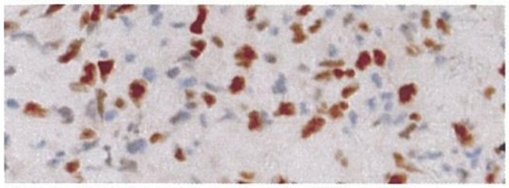
- Gross: Moderately vascular and firm
- Morphology: Embryonal or alveolar, less commonly pleomorphic
- No confirmed cases of spindle cell/sclerosing intracerebral rhabdomyosarcomas, but some parameningeal cases are reported
  - ➢ Varying proportions of undifferentiated small cells
  - ➢ Embryonal: Rhabdomyoblasts within a loose myxoid mesenchyme
  - ➢ Alveolar: Highly cellular, primitive round cells

OTHER HIGH YIELD POINTS

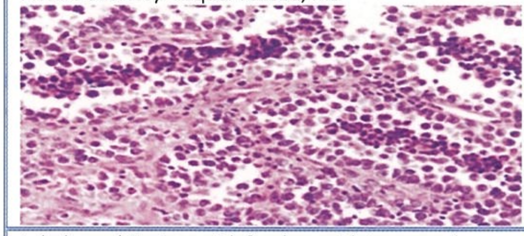
- Clinical:
  - ➢ Mostly in **children,** rare in adults
  - ➢ Embryonal rhabdomyosarcoma has been seen in patients with Gorlin syndrome (nevoid basal cell carcinoma syndrome)
  - ➢ Can be seen at the cerebellopontine angle or optic nerve; there **is no stereotypical location**
- Immunohistochemistry:



MYOD1



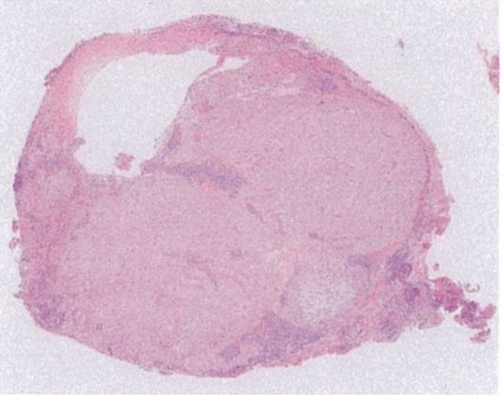
Alveolar rhabdomyosarcoma with PAX3::FOXO1
Picture courtesy: Raquel Yokoda, MD



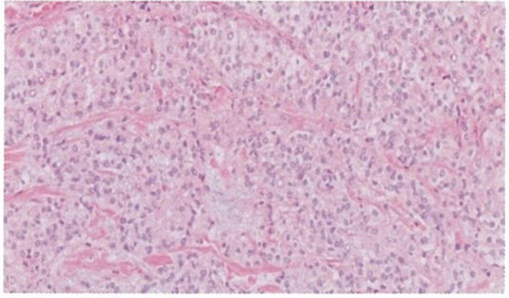
- **(+) MYOD1, desmin**
- Myogenin positive (diffuse in alveolar type and scattered in embryonal type)
- OLIG2 positive (as the systemic FOXO1 fusion)
- Pitfall: OLIG2 does not represent a glial component in these tumors

- Molecular:
  - **Alveolar: PAX3::FOXO1 or PAX7::FOXO1 fusion**
  - Children: Spindle and sclerosing = NCOA2 and VGLL2
  - Older children and adults = MYOD1 mutations
  - Embryonal and pleomorphic with no specific mutation, but embryonal often displays whole chromosome gain (usually chromosome 8)
- Differential diagnosis:
  - DICER1-mutant intracranial sarcoma
  - CNS metastasis from systemic primary rhabdomyosarcomas
- Prognosis:
  - Poor, due to recurrence
  - Overall survival > 24 months is exceptional
  - Not currently staging CNS 5 WHO

Lobular architecture with focal myxoid stroma and lymphoplasmacytic rim
Picture courtesy: Raquel Yokoda, MD



Areas of meningothelial-like cells with optically empty nuclei
Picture courtesy: Raquel Yokoda, MD



Angiomatoid vessels
Picture courtesy: Raquel Yokoda, MD

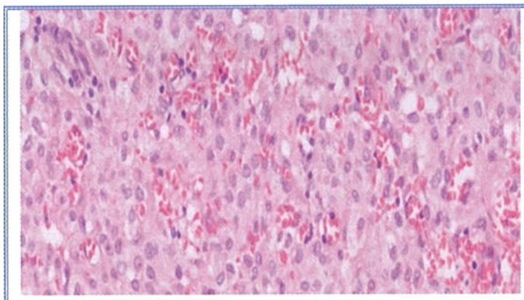
INTRACRANIAL MESENCHYMAL TUMOR, FET::CREB FUSION POSITIVE

MORPHOLOGY

- Gross: Partially encapsulated, tan-brown, gelatinous, hemorrhagic
- Variable morphology
  - Myxoid to collagenous stroma
  - Sheets, cords, or lobules of tumor cells
  - Spindled cells, epithelioid cells, rhabdoid cells, clear cells, or small round blue cells are possible
  - Small, dilated vessels (angiomatoid)
  - Low mitotic index
  - Vague whorling

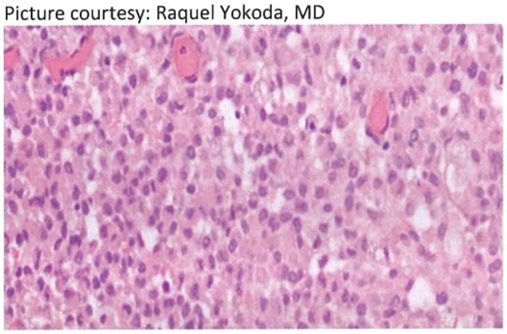
OTHER HIGH YIELD POINTS

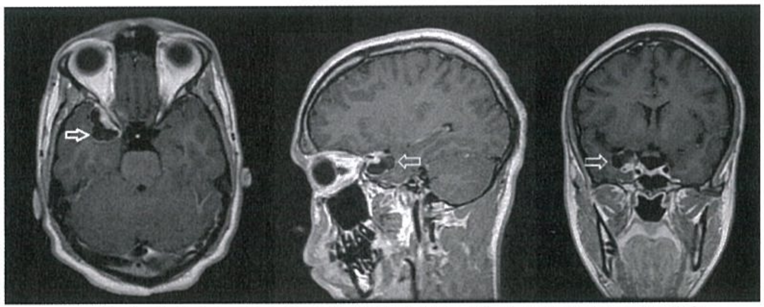
- Clinical:
  - Mostly **children** and **young adults**
  - **Supratentorial** > infratentorial
  - **Extra-axial** (attached to dura/meninges or intraventricular) > intra-axial
  - Slow-growing tumor with a high recurrence rate
- Immunohistochemistry:
  - **(+) CD99, EMA, desmin,** CD163, CD68 (diffuse or patchy)
  - SMARCB1 (INI1) and SMARCA4 (BRG1) retained
  - Ki-67 index low
- Reticulin stain highlights intercellular matrix
- **Fusions between FET family of RNA-binding proteins (EWSR1, FUS) and CREB family of transcription factors (CREB1, ATF1, CREM)**
- Also known as angiomatoid fibrous histiocytoma
- Radiology:
  - Well circumscribed
  - Large, lobulated, cystic, contrast enhancing
  - Intratumoral hemorrhage and peritumoral edema
  - **Dural based**
  - May mimic meningioma



Focally rhabdoid

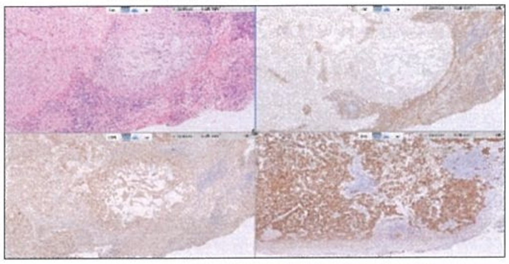
Picture courtesy: Raquel Yokoda, MD

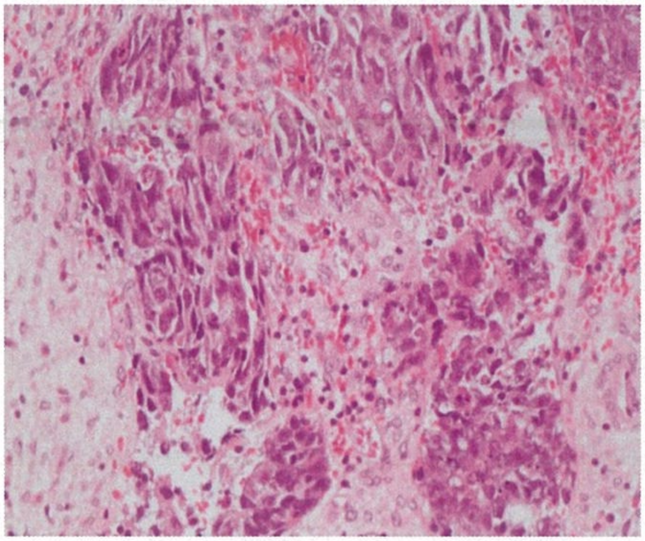




Brain MRI showing a sphenoid wing extra-axial lesion in a young adult

H&E, EMA, CD99, and desmin





GERM CELL TUMORS

SADHNA AHUJA, MD
LAKSHMI RAMACHANDRAN NAIR, MD

16. GERM CELL TUMORS

GERM CELL TUMORS

PRIMARY DIAGNOSTIC ENTITIES

Teratoma
- **Mature Teratoma**
- **Immature Teratoma**
- **Teratoma with malignant transformation**

Germinomas

Non-germinomatous germ cell tumors
- **Embryonal carcinoma**
- **Yolk sac tumor**
- **Choriocarcinoma**

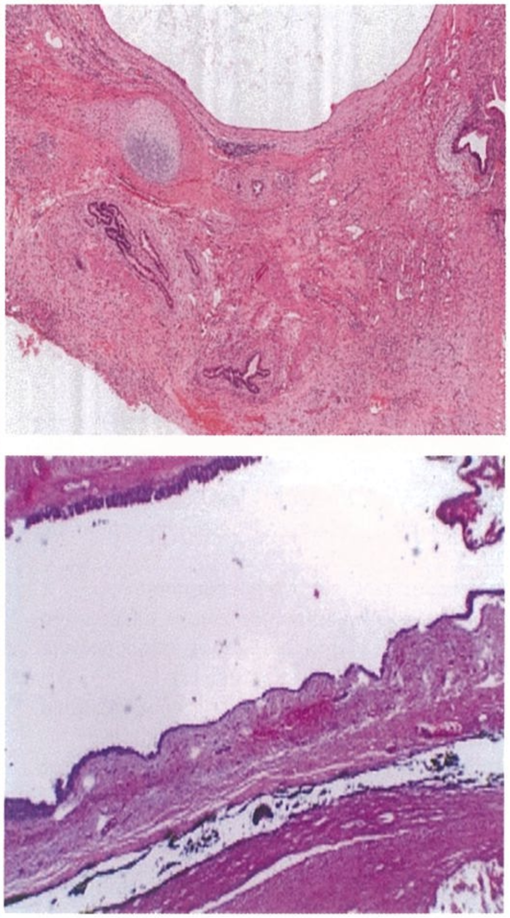
Mixed germ cell tumors

Imaging:
- Heterogenous solid and cystic contrast enhancing on T2 weighted images. (Cystic component is non-enhancing)
- Rarely appear as diffuse enhancement in periventricular regions
- Calcifications are commonly seen (esp. in pineal regions)

KEY FACTS

- Group of tumor cells arising from pluripotent germ cells with embryonic or extraembryonic component
- Morphologically and immunophenotypically like gonadal and extra neuraxial tumors
- There is no precursor lesion in the CNS germ cell tumor (carcinoma in situ/intratubular germ cell neoplasia)
- 0.1 to 3.4% of all primary intracranial neoplasms in Western countries (15% in East Asia and Japan)
- Increase incidence in males (three times higher than females)
- The majority are located in the midline (**Pineal region most common**), followed by the suprasellar region
- **Presentation:**
  - Perinaud syndrome (Pineal region)
  - Precocious puberty (Pineal region)
  - The diagnostic triad of diabetes insipidus, visual acuity loss and hypopituitarism (Suprasellar region)

Mature teratoma with cartilaginous and gastric differentiation



Picture and radiology image courtesy: Dr.Silvia J. Hernandez

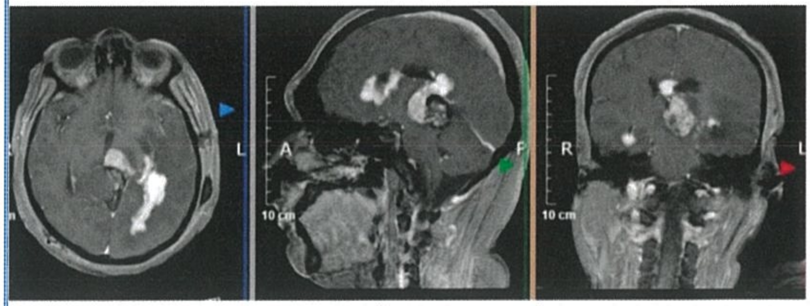
MATURE TERATOMA

MORPHOLOGY

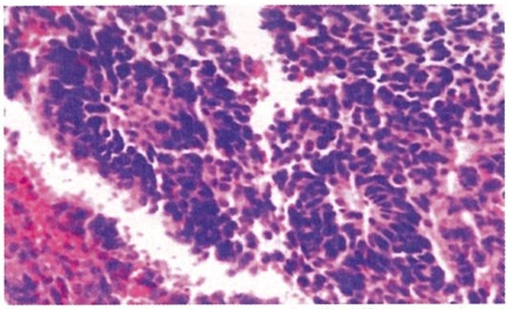
- Fully differentiated derivatives of trilinear germ cell layer arranged in a disordered pattern
  - Ectoderm (skin, hair)
  - Neuroectoderm (brain tissue, choroid plexus)
  - Mesoderm (cartilage, adipose tissue)
  - Endoderm (Glandular epithelium resembling respiratory and gastrointestinal tract)

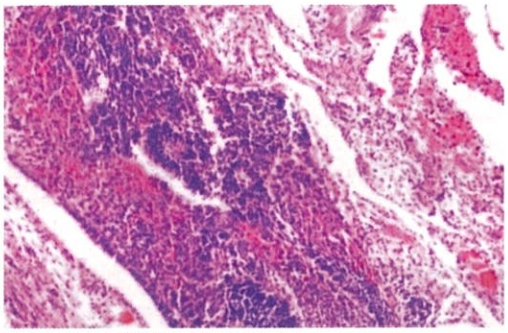
OTHER HIGH YIELD POINTS

- Focal mitosis and increased cellularity can be seen (do not over diagnose as immature teratomas)
- Normal levels of LDH, AFP and Beta hCG
- IHCs: Pancytokeratin is positive in the epithelial component
- Be aware of the mature brain cerebellar tissue to be confused with an immature component of teratoma
- **Surgically curable**
- Absence of another germ cell tumor

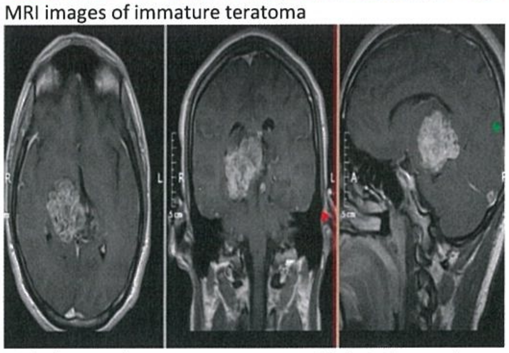


MRI images showing a midline contrast-enhancing teratoma


Immature teratoma with incompletely differentiated areas



MRI images of immature teratoma


Radiology and picture courtesy: Dr. Silvia J. Hernandez

IMMATURE TERATOMA

MORPHOLOGY

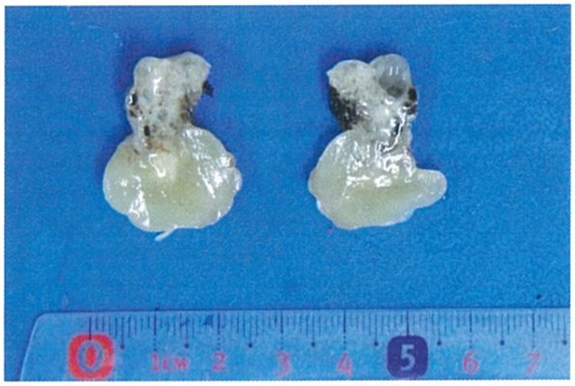
- Partially differentiated/incompletely differentiated embryonic type tissue that has ability to convert into ectoderm, endoderm, and mesoderm
- May observe mixture of mature elements
- Look for blastema like stroma encasing immature glands
- Look for areas with abundant mitosis and apoptosis
- Look for fetal type tissue (cartilage, bone, adipose tissue)

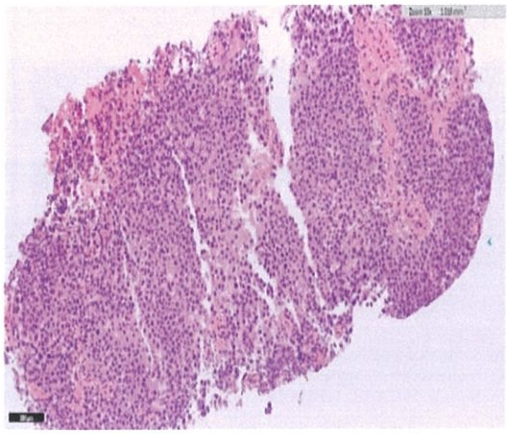
OTHER HIGH YIELD POINTS

- Extensive sampling is the key
- Absence of another germ cell tumor
- Grading based on the immature component (Grade 1-3) can be done like ovarian counterparts, but significant amplitude of grading has not been observed in the CNS
- **Immature teratoma can undergo adult type somatic maturation after chemoradiation**

TERATOMA WITH SOMATIC TYPE MALIGNANCY

- Mature or immature type teratoma with secondary development of somatic type epithelial (carcinoma) or mesenchymal (sarcoma) malignancy
- Must rule out high grade neuroepithelial tumors or medulloblastoma




Sheets of monomorphic tumor cells in a case of germinoma

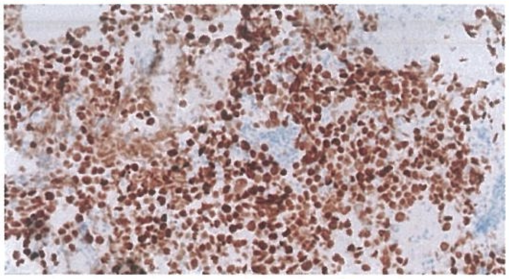
GERMINOMA

MORPHOLOGY

- Nests of **large monomorphic tumor cells** with clear to eosinophilic cytoplasm, prominent nucleoli encased by fibrin rich septae containing **reactive T lymphocytes**
- Individual cell necrosis or areas of confluent necrosis are common
- Florid non-caseating granulomatous type inflammation can be observed in some cases, and differential diagnosis of granulomatous infection and sarcoidosis can be entertained (look for malignant tumor cells)
- Occasionally, syncytiotrophoblast type giant cells may be present and should not be over diagnosed as choriocarcinoma
- Frozen crush smear is very helpful but extensive nuclear crushing may occur and actual tumor cells may be difficult to visualize

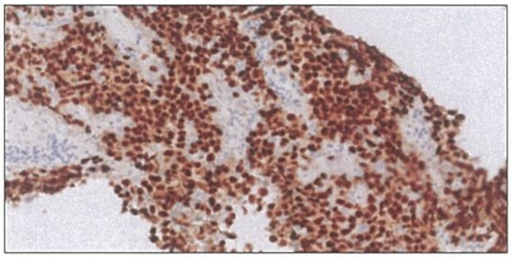
OTHER HIGH YIELD POINTS

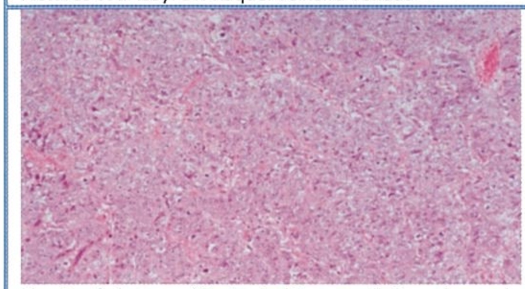
- **Most common germ cell tumor**
- Imaging may show homogenous enhancement or tumor may decorate the subependymal lining of the lateral ventricles
- IHC: **CD117+, SALL4+, OCT3/4+,** CD30-
- Beta hCG and LDH levels are elevated, AFP is normal
- **Highly radiosensitive tumor**



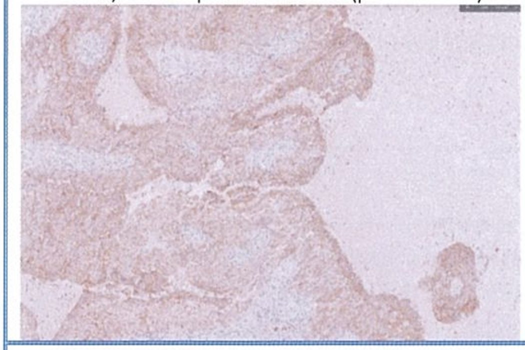
SALL4 stain diffusely positive in germinoma
Pictures courtsey: Dr. Raquel Teixeira Yokoda

Oct3/4 diffusely positive in germinoma





Sheets of pleomorphic atypical tumor cells in embryonal carcinoma, which is positive for CD30 (picture below)



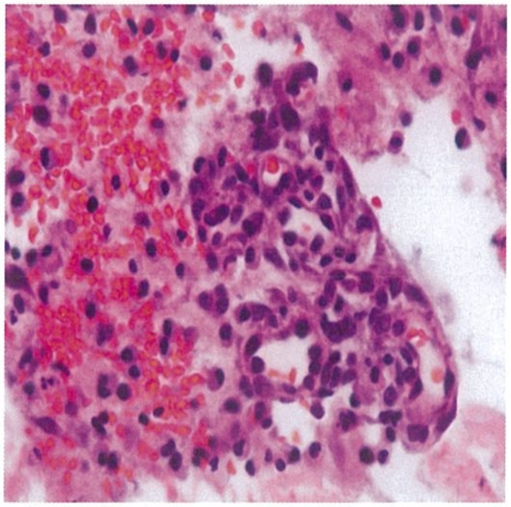
EMBRYONAL CARCINOMA

MORPHOLOGY

- Multiple growth patterns in same tumor (solid, glandular, and papillary)
- OCT 3/4, CD30 positive, cohesive epithelioid, anaplastic tumor cells with relatively indistinct cytoplasmic membranes (syncytial formation) with granular moderate cytoplasm that can have basophilic, amphophilic or eosinophilic hue, overlapping nuclei and macro nucleoli
- Necrosis, hemorrhage, mitosis, and apoptosis frequently encountered

OTHER HIGH YIELD POINTS

- IHC: **CD30+,** OCT3/4+, SALL4+, Beta hCG-
- **Beta hCG level is normal**
- **LDH and AFP are increased**
- Applique' pattern: Degenerated, dark, smudgy embryonic tumor cells often present at the periphery may be mistaken as syncytiotrophoblastic cells and confused with diagnosis of choriocarcinoma (Increased hCG, negative OCT 3/4, negative CD30, and biphasic pattern helps to differentiate)



Yolk sac tumor showing vague microcystic areas
Picture courtesy: Dr. Raquel Teixeira Yokoda

YOLK SAC TUMOR

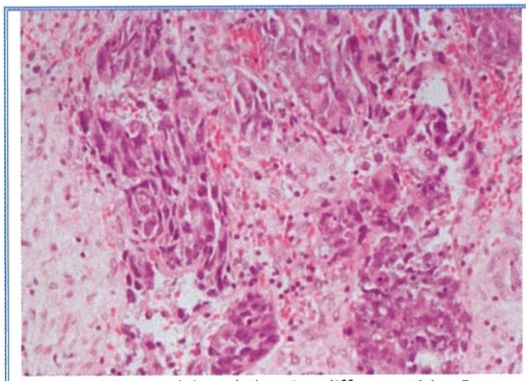
MORPHOLOGY

- Combination of histological patterns are seen (reticulate and microcystic are the most common types)
- **Schiller Duval body** (centered blood vessel encased by cuboidal or columnar lined papillae) rare but pathognomonic finding
- Large tumor cells with distinct cytoplasmic membrane, PAS positive diastase resistant eosinophilic intracytoplasmic (and or extra cytoplasmic) **hyaline eosinophilic globules** with monotonous, non-overlapping conspicuous to inconspicuous nucleoli arranged in loose matrix

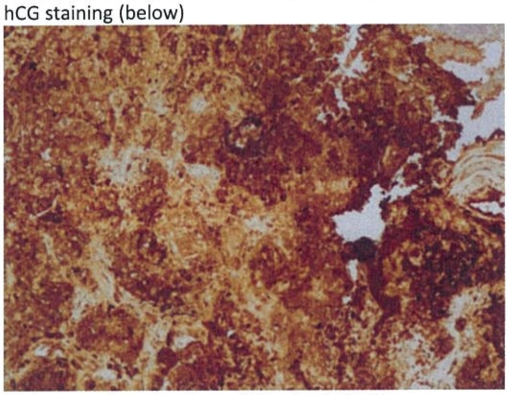
OTHER HIGH YIELD POINTS

- **Increased alpha fetoprotein** levels
- Normal LDH and beta hCG levels
- **Pure form is rare**, majority a component of mixed germ cell tumor
- IHC: **SALL4+, Glypican 3+, OCT3/4-,** CD30 -
- Tumor recapitulates the primitive phases of yolk sac development, allantois, or extraembryonic mesenchymal tissue

16. GERM CELL TUMORS



Choriocarcinoma (above) showing diffuse positive Beta hCG staining (below)



Picture courtesy: Dr. Raquel Teixeira Yokoda

CHORIOCARCINOMA

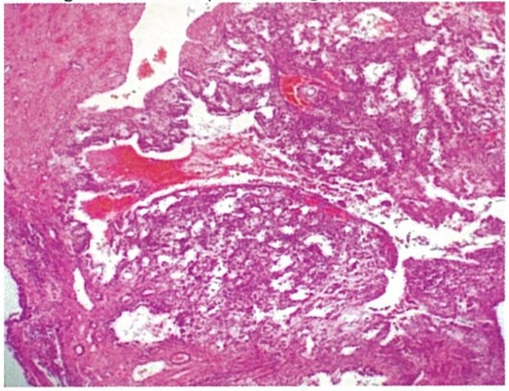
MORPHOLOGY

- Biphasic tumor composed of core of mononucleated cytotrophoblasts and syncytiotrophoblasts (often kissing the cytotrophoblast cells)
- Both components are required for the diagnosis
- Blood filled pools with extensive areas of necrosis
- Cytotrophoblast
  - ➢ Homogenous, monomorphic population of tumor cells with prominent clear to vacuolated cytoplasm and vesicular nuclei
  - ➢ Frequent mitosis and atypia are seen
  - ➢ Positive for pancytokeratin (AE1/AE3), SALL4 and CD10
  - ➢ Prominent proliferation of intermediate trophoblasts can occur and can be mistaken for carcinoma (IHC can help)
- Syncytiotrophoblast
  - ➢ Dark smudgy tumor cells with vesicular nuclei, often with varied morphology
  - ➢ Look for stretched spindle cells rimming the vascular channels
  - ➢ Mitosis rare
  - ➢ Positive for pancytokeratin (AE1/AE3), inhibin, HCG and CD10)

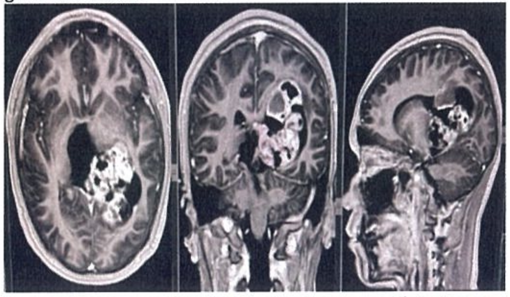
HIGH YIELD POINTS

- The least common and the highly malignant germ cell tumor
- IHC: **SALL4+, Pancytokeratin +, Beta hCG+, CD10+, Inhibin +, OCT3/4-**
- **Increased Beta hCG levels** and normal LDH and AFP
- Treated tumors (after adjuvant therapy) can show monophasic pattern

Mixed germ cell tumor photomicrograph



MRI images showing a contrast-enhancing midline mixed germ cell tumor



Histology and radiology image courtesy: Dr. Silvia J. Hernandez

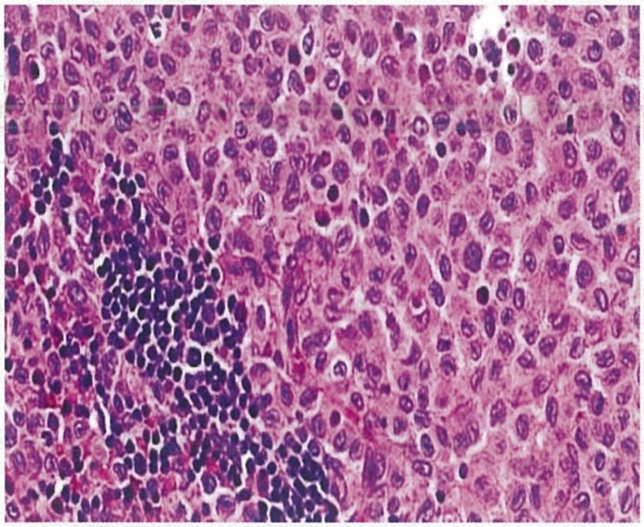
MIXED GERM CELL TUMORS

MORPHOLOGY

- Germ cell tumors which are combination of any histological types as stated above (**quantify each germ cell tumor component** in the report)
- Most **common combination type is Teratoma with Germinoma**

OTHER HIGH YIELD POINTS

- There is no prognostic difference in patients presenting before or after puberty (unlike germ cell tumor the testis)
- If any ectodermal or hepatic component is seen, then look for yolk sac tumor closely
- Blastema like component in immature teratoma shows many mitoses and apoptoses
- Germinoma should be in the differential diagnosis if young adolescent or pediatric patient presents with exuberant granulomatous inflammation in the suprasellar region
- Molecular diagnostic methods play minor role
  - ➢ Germinoma: Low DNA methylation profile
  - ➢ Non-germinomatous germ cell tumor: High DNA methylation profile
  - ➢ Both **Germinoma and non-germinomatous germ cell tumor show somatic alterations in MAPK/PI3K pathway**
- If non-germinomatous germ cell tumor is seen in the cerebral hemispheres, consider the possibility of metastatic from extracranial sites
- Patient with chromosomal abnormalities such as Klinefelter syndrome or Down syndrome have slightly increased risk
- **Growing teratoma syndrome:** A phenomenon happens in the mixed germ cell tumors where malignant component responds to adjuvant therapy while mature teratoma does not respond

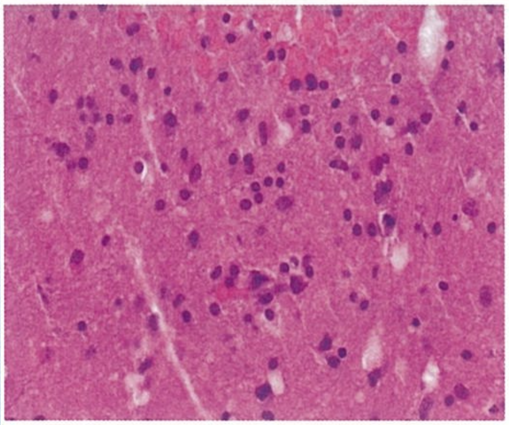


HEMATOLYMPHOID TUMORS

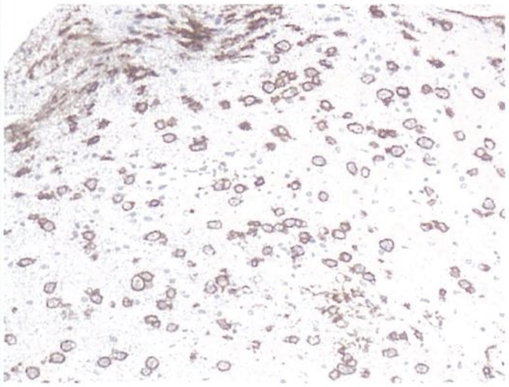
AISHWARYA RAVINDRAN, MD

17. HEMATOLYMPHOID TUMORS

CNS LYMPHOMAS



H&E sections showing diffuse infiltration of brain parenchyma by large CD20-positive B-cells



IHC: CD20

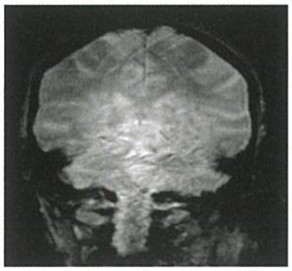
PRIMARY DIFFUSE LARGE B-CELL LYMPHOMA OF THE CNS

MORPHOLOGY

- Large, atypical B-lymphocytes with round to oval/irregular nuclei, distinct nucleoli, and moderate to abundant cytoplasm; they typically show **perivascular pattern of growth,** although may present in a diffuse pattern
- Tumor cells admixed with reactive small lymphocytes

OTHER HIGH YIELD POINTS

- The B-cells are positive for CD19, CD20, PAX5, CD22, CD79a with a **majority** co-expressing **BCL6 and MUM1**; **< 10% of cases express CD10**
- CD10 positivity, although rare, should prompt investigation into a systemic DLBCL with secondary involvement of CNS
- **EBV** is usually negative; **positivity in the large B-cells** should prompt clinical **evaluation for immunodeficiency**
- The tumor B-cells are **highly susceptible to corticosteroid therapy,** which might result in extensive necrosis and no viable tumor cells
- **Worse prognosis than systemic DLBCL**; however, a minor proportion of younger patients may be cured
- Genetic alterations result in proliferation and prevent apoptosis; common genes involved include CD79B (in 20-83% of cases), INPP5D (in 25%), CBL (in 4%), BLNK (in 4%), CARD11 (in 16%), MALT1 (in 43%), BCL2 (in 43%), and MYD88 (in > 50%)



MRI brain with contrast depicting a diffuse, extensive T2/FLAIR hyperintense signal involving the bilateral basal ganglia, thalami, and midbrain and extending to the posterior tegmentum of the pons

IMMUNODEFICIENCY-ASSOCIATED CNS LYMPHOMAS

MORPHOLOGY

- Typically **EBV-related**; usually large B-cells with irregular nuclei involving the brain parenchyma

OTHER HIGH YIELD POINTS

- Immunophenotypically, the B-cells are positive for CD19, CD20, PAX5, CD22, and CD79a with **co-expression of EBV (including EBNA1-6, EBER-ISH, LMP1)**
- Occur in the setting of **inherited or acquired immunodeficiency** (AIDS, iatrogenic causes including post-transplant setting); **associated immunodeficiency syndromes** include ataxia telangiectasia, Wiskott-Aldrich syndrome, IgA deficiency
- EBV-positive DLBCL of the elderly is related to immunosenescence and occurs in patients aged > 50 years
- Poor prognosis

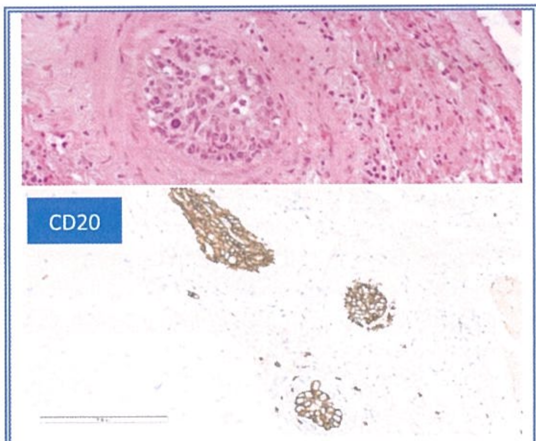
LYMPHOMATOID GRANULOMATOSIS

MORPHOLOGY

- **Angiodestructive lymphoproliferative** disorder composed of **polymorphous lymphoid infiltrates with frequent, singly distributed, large, EBV-positive B-cells** in a rich background of T-cells (a mixed population of CD4- and CD8-positive T-cells)
- The **EBV-positive B-cells co-express CD20 and CD30 (majority positive)**
- Grading of lymphomatoid granulomatosis depends on the number of EBV-positive and CD20-positive B-cells
    - **Grade 1: < 5 cells/HPF**
    - **Grade 2: 5-50 cells/HPF**
    - **Grade 3: > 50 cells/HPF**

OTHER HIGH YIELD POINTS

- **Multiple focal intraparenchymal lesions**; other sites of involvement include leptomeninges, cranial nerves, and spinal cord
- MRI: **Mass lesions throughout CNS**; multiple punctate lesions along perivascular and periventricular spaces may be present
- **Large aggregates/sheets of EBV-positive, large B-cells** should prompt classification as **EBV-positive diffuse large B-cell lymphoma**
- **Aggressive** clinical course; management similar to diffuse large B-cell lymphoma including corticosteroids, radiation, or chemotherapy



Intravascular growth of atypical large CD20-positive B-cells
Picture courtesy: Lakshmi Ramachandran, MD

INTRAVASCULAR LARGE B-CELL LYMPHOMA

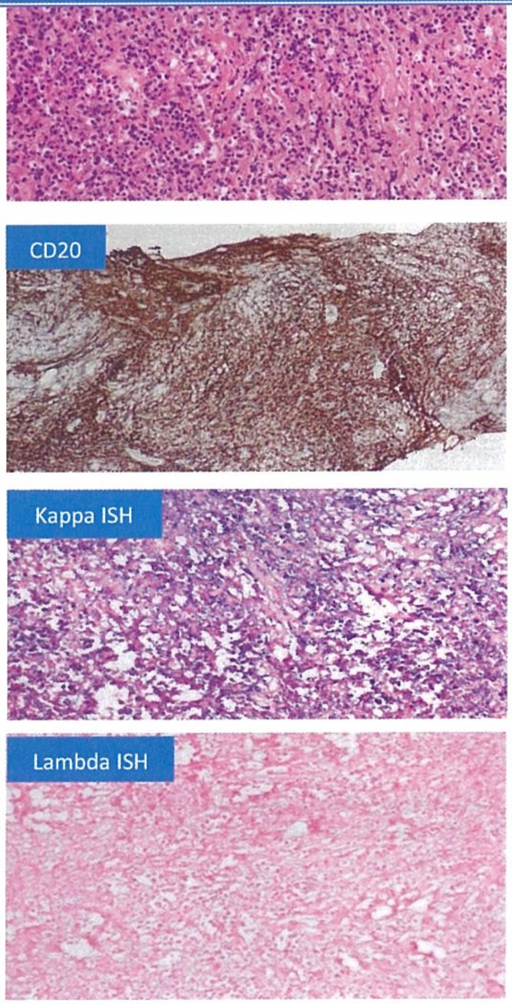
MORPHOLOGY

- **Aggressive B-cell lymphoma** characterized by **exclusive intravascular growth composed of atypical B-cells** highlighted by immunostaining for CD20, CD79a, and PAX5

OTHER HIGH YIELD POINTS

- Median age: 70 years (range: 34-90); equal prevalence in males and females
- Poor prognosis; usually **widely disseminated**, and systemic staging is essential
- **Absence of CD29 and CD54 (ICAM1) expression** results in inability of tumor cells to migrate transvascularly
- **Decreased expression of chemokine receptors** (CXCR5, CCR6, CCR7) while MMP2 and MMP9 are not expressed results in tumor cell adhesion to endothelium
- **Methotrexate-based chemotherapy** may be beneficial in a subset of patients

MISCELLANEOUS RARE LYMPHOMAS IN THE CNS



Dura showing diffuse lymphoplasmacytic infiltrates with numerous CD20-positive B-cells associated with extensive kappa light chain-restricted plasma cells by in situ hybridization (ISH); these are negative for lambda ISH

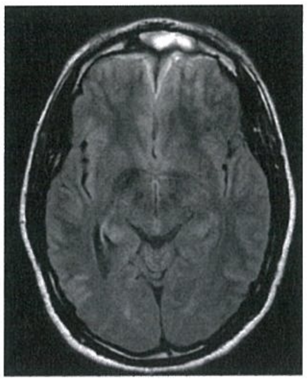
MALT LYMPHOMA OF THE DURA

MORPHOLOGY

- **Low-grade B-cell lymphoma** composed **of small B-cells** with slightly irregular nuclei, indistinct nucleoli, and moderate cytoplasm; **plasmacytic differentiation** may be present
- **Areas of plasmacytic differentiation** may show monotypic staining for kappa or lambda light chains

OTHER HIGH YIELD POINTS

- The B-cells are positive for **CD19, CD20, PAX5, BCL2,** and are negative for CD5, CD10, cyclin D1, CD23, and BCL6; MUM1 is positive in a majority of cases
- **Good prognosis** with **complete remission** usually; treated with resection, radiation, and/or chemotherapy
- Local and systemic relapses are rare
- **Clonal immunoglobulin gene rearrangements are typically necessary** in the absence of aberrant immunophenotype to distinguish from reactive marginal zone hyperplasia
- Genetic alterations: Trisomy 3, TNFAIP3 mutation or deletion, activating NOTCH2 mutations with concurrent inactivating TBL1XR1 mutations, recurrent gains of 6p25.3, losses at 1p36.32
- IGH translocation and MALT lymphoma-associated translocation are rare



Dural-based tumors along the anterior falx and over the left frontal and frontoparietal convexity

OTHER LOW-GRADE B-CELL LYMPHOMAS OF THE CNS

MORPHOLOGY

- Analogous to systemic low-grade B-cell lymphomas, **most commonly extranodal marginal zone lymphoma**; others include **chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), lymphoplasmacytic lymphoma, follicular lymphoma, or low-grade B-cell lymphomas, not otherwise specified**

OTHER HIGH YIELD POINTS

- Most common immunophenotype similar to MZL: (+) CD19, CD20, BCL2; (-) CD5, CD10, cyclin D1, BCL6; monotypic plasma cells for kappa or lambda
- Can affect any portion of brain parenchyma presenting as a **solitary lesion, multiple discrete lesions, or diffuse lymphomatous lesions**
- Clonal immunoglobulin gene rearrangements present
- **Better prognosis than the primary diffuse large B-cell lymphomas**
- Rarely progress to systemic disease

ANAPLASTIC LARGE CELL LYMPHOMA (ALK-POSITIVE/ALK-NEGATIVE)

MORPHOLOGY

- Diffuse proliferation of large atypical cells with abundant cytoplasm, **including hallmark cells** with bean-shaped nuclei and an eosinophilic perinuclear area
- Cerebrospinal fluid may show involvement by large atypical neoplastic cells with cytoplasmic azurophilic granules

OTHER HIGH YIELD POINTS

- Tumor cells **positive for CD30 and EMA**; may express one or more T-cell markers; sometimes they are T-null phenotype (negative for all T-cell markers)
- ALK-positive ALCL: ALK-positive by immunohistochemistry
- Most common translocation in ALK-positive ALCL involves **t(2;5)** resulting in **NPM1::ALK** fusion
- **ALK-positive ALCL similar or worse prognosis to systemic ALK-positive ALCL**; sustained remission can occur in a subset of cases
- **ALK-negative ALCL** typically harbors genetic alterations involving the JAK/STAT3 signaling pathways and usually has **a poor prognosis**

T-CELL AND NK/T-CELL LYMPHOMAS

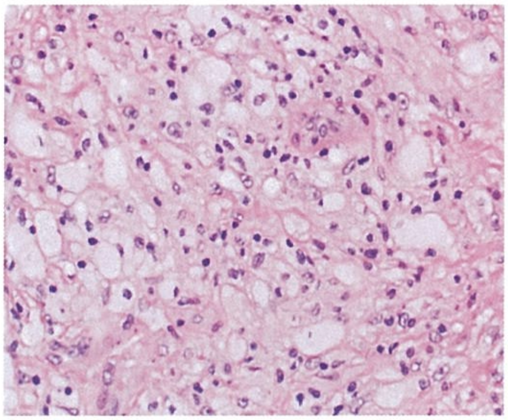
MORPHOLOGY

- Majority involving the CNS are PTCL-NOS (peripheral T-cell lymphoma, not otherwise specified) characterized by small to intermediate or large atypical T-cells with frequent perivascular growth pattern and areas of necrosis
- They are accompanied by reactive gliosis and a histiocytic reaction

OTHER HIGH YIELD POINTS

- These T-cells are positive for CD3, CD8 >> CD4, TCR-beta >>> TCR-gamma, and usually express ≥ 1 cytotoxic granule proteins (TIA1, granzyme B, perforin); tumor cells are negative for CD56 in PTCL-NOS
- CD2, CD5, and/or CD7 are variable (lost in subset of cases)
- Extranodal NK/T-cell lymphomas are positive for CD3, CD56, cytotoxic granule proteins, and EBV-encoded small RNA (EBER); they are negative for CD5 and B-cell antigens; CD30 expression may be present
- Variable prognosis in PTCL-NOS
- Poor prognosis in cases with extranodal NK/T-cell lymphoma

HISTIOCYTIC TUMORS



H&E showing sheets of foamy histiocytes

ERDHEIM-CHESTER DISEASE

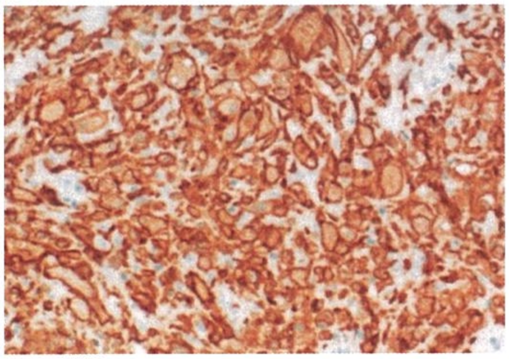
MORPHOLOGY

- **Foamy/xanthomatous histiocytes** with bland nuclei associated with Touton giant cells and dense fibrosis; however, CNS lesion may have heterogeneous manifestations
- Spare lymphoplasmacytic infiltrates

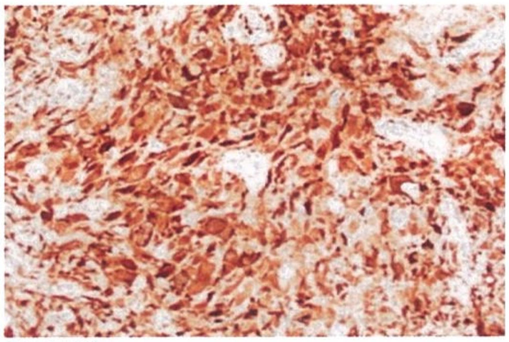
OTHER HIGH YIELD POINTS

- **Positive for monocyte/macrophage markers** (CD4, CD14, CD68, CD163), factor XIIIa, fascin, S100 (variable)
- **Frequent phosphorylated ERK expression**, which signifies activation of the MAPK pathway
- **Positive for BRAF V600E in roughly 50-60% of cases**
- Negative for OCT2, ALK, CD1a, langerin
- **Heterogeneous multisystemic disease** with **nervous system** manifestations occurring in **about 40% of cases** that may result in ataxia, dysarthria, cognitive impairment, headaches, or peripheral neuropathy

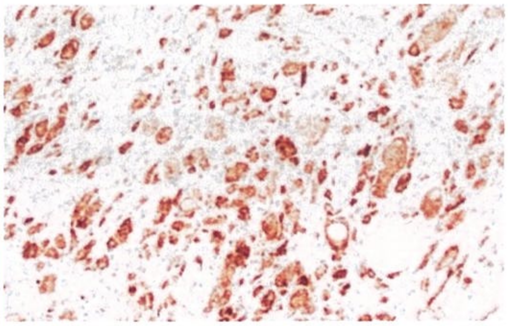
CD163



Factor XIIIA

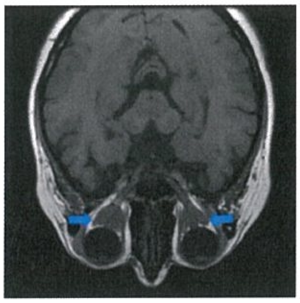


BRAF V600E



H&E section of orbit involved by foamy (xanthogranulomatous) histiocytic infiltrates that are positive for CD163, factor XIIIa, and BRAF V600E

- **Endocrine manifestations** include **central diabetes insipidus (25-50% of cases)** and **may precede the ECD diagnosis by several years**, sometimes even decades; an **abnormal MRI of the pituitary stalk** may be helpful in such cases
- **Orbital involvement (about 30% of cases)** usually manifests as **a mass-like lesion involving the intraconal space**, often bilaterally; it may be subclinical or result in symptomatic retro-orbital pain and proptosis, with possible progression to oculomotor nerve palsy and vision loss
- Associated periorbital skin involvement presenting as **xanthomatous papulonodules and indurated plaques** with or without associated pruritus may occur
- **Other manifestations of ECD:**
  - ➢ **Bone pain** is a common presenting symptom associated with **bilateral symmetric osteosclerosis of metadiaphysis of the femur, tibia, and fibula** (~95% cases)
  - ➢ **Retroperitoneal involvement** (~40-50%) may frequently present as an incidental finding characterized by perinephric soft tissue thickening extending to the adrenals, classically known as **"hairy kidney"**
  - ➢ **Cardiovascular involvement** (~40-70%) is characterized by an infiltrative right atrial mass and **"coated aorta"** with adventitial-based thickening of the thoracoabdominal aorta
  - ➢ **Lung involvement** may occur in ~50% of cases with variable presentations such as pleural thickening, interlobular septal thickening, ground-glass opacities, and solid masses; pulmonary function tests may show a more **restrictive** than obstructive lung disease pattern
- Management includes surgery, **cladribine**, immunomodulators, and **molecular-targeted therapies** including **BRAF inhibitors and MEK inhibitors**
- **Neurodegenerative lesions** are **relatively resistant** to therapeutic interventions



A T1 MRI of the orbits without contrast demonstrates bilateral soft tissue masses within the intraconal orbits (arrows)
Picture courtesy: Jason R. Young, MD

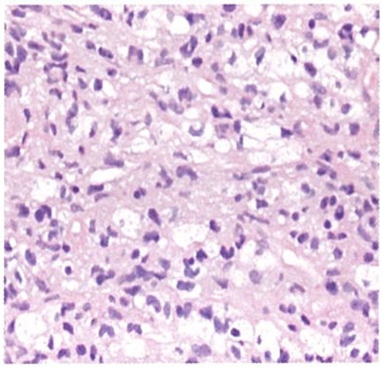
JUVENILE XANTHOGRANULOMA

MORPHOLOGY

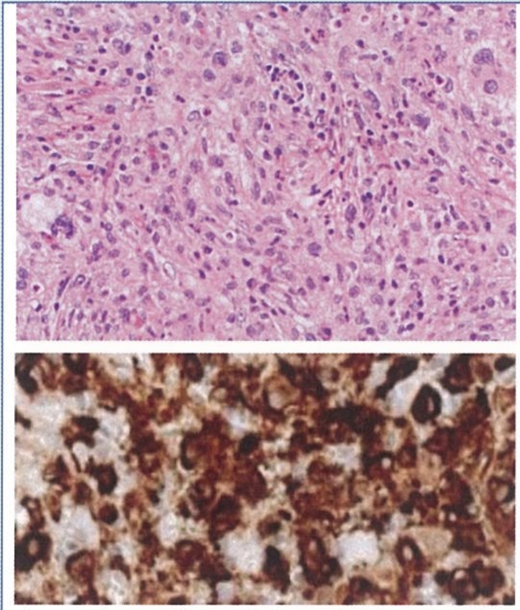
- Grossly non-encapsulated, circumscribed lesions composed of large **xanthomatous/foamy histiocytes with bland nuclear features** and **Touton giant cells**
- Occasionally, lesions may be composed of spindled, epithelioid, and/or oncocytic histiocytes
- Mitoses may be present
- **Inflammatory background** with a mixed population of lymphocytes, eosinophils, plasma cells, neutrophils, and mast cells

OTHER HIGH YIELD POINTS

- Positive for **monocytic/histiocytic markers** (CD4, CD14, CD68, CD163), factor XIIIa, and fascin



- **Variable S100 expression**
- Negative for Langerhans cell markers (CD1a and langerin) and ALK
- **Benign cephalic histiocytosis:** A clinical subtype of JXG that is **self-resolving**, presents as papular eruption predominantly in the head and neck of young children
- **< 5% may be systemic JXG**, including CNS involvement, that may present as **seizures**, hydrocephalus, diabetes insipidus; bone marrow involvement presents with cytopenias
- **MAPK/ERK pathway alterations** including NRAS, KRAS, ARAF, MAP2K1, CSF1R mutations
- **PIK3CD mutations** suggest a pathogenetic role of the PI3K pathway
- RNF1::BRAF and NTRK1 fusions
- Systemic JXG with CNS involvement may be associated with BRAF V600E mutation; however, Erdheim-Chester disease needs to be excluded by clinical correlation
- **Excellent prognosis except in disseminated JXG**
- Usually, **self-resolving cutaneous lesions**
- Variable response rates to clofarabine, cladribine, and/or cytarabine; targeted therapy can be utilized in those with MAPK pathway mutations


Pleomorphic HS cells positive for CD163

HISTIOCYTIC SARCOMA

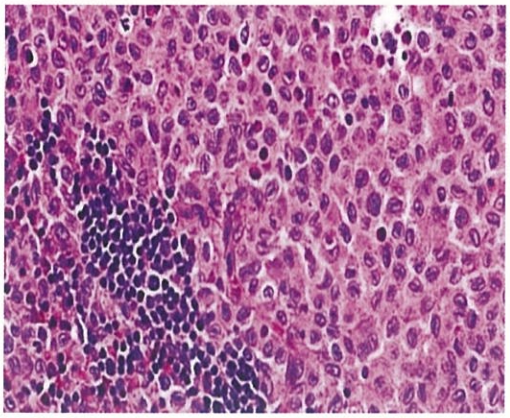
MORPHOLOGY

- **Non-cohesive, large pleomorphic cells** with abundant eosinophilic cytoplasm
- Hemophagocytosis may be present

OTHER HIGH YIELD POINTS

- Positive for at least **2 histiocytic markers: CD163, CD68, CD4, PU.1**; other positive IHC markers include **lysozyme, CD31, CD45, S100 (variable)**
- **Negative for CD1a, langerin, and ALK as well as melanoma** (SOX10, HMB-45), **follicular dendritic** (CD21, CD23, CD35), **epithelial** (cytokeratins), **vascular** (ERG), **mature B-cell** (CD20, PAX5), and **T-cell** (CD3) markers
- **Clonal immunoglobulin gene rearrangements** in cases with **prior history of B-cell lymphoma** suggest **transdifferentiation**
- **MAPK pathway alterations**, including BRAF V600E mutations, have been described
- **Mutations in tumor suppressors** (CDKN2A, TP53) are common
- PI3K pathway alterations include PTEN, MTOR, PIK3R1, PIK3CA, CSF1R
- BRAF and NTRK1 rearrangements
- **Treatment is individualized** for each patient, depending on extent of disease
- **Aggressive neoplasm** with poor response to therapy
- Localized tumors have favorable outcomes

Sheets of round to oval histiocytes with grooved nuclei and admixed inflammatory infiltrate

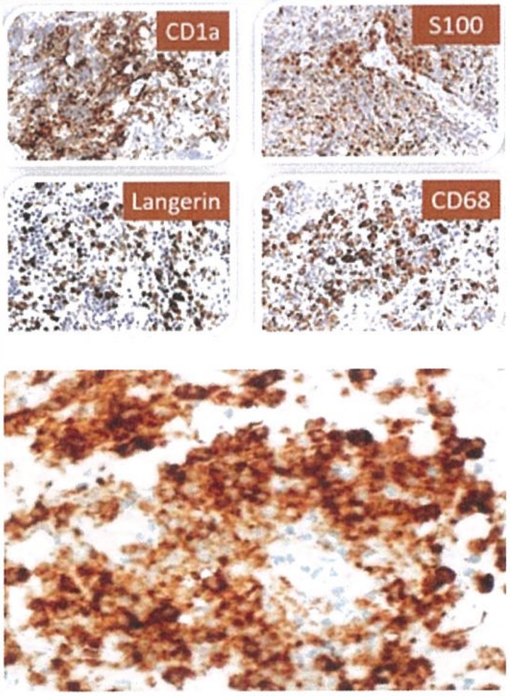


LANGERHANS CELL HISTIOCYTOSIS

MORPHOLOGY

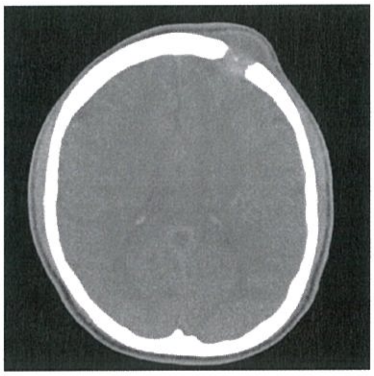
- Morphology is characterized by **large, round/oval histiocytes with grooved nuclei**, inconspicuous nucleoli, and moderate to abundant pale, eosinophilic cytoplasm
- The **inflammatory milieu** consists of **frequent eosinophils** admixed with lymphocytes, reactive macrophages, rarely neutrophils, and plasma cells
- **Minimal to no nuclear atypia,** occasional mitoses without associated atypical figures
- Central necrosis may be present but is of **no prognostic significance**
- Presence of **tennis racket-shaped Birbeck granules** in the cytoplasm on ultrastructural examination
- Positive for **CD1a, langerin, CD68 (Golgi-like or dot-like)**, S100
- **Langerin positivity is a surrogate of Birbeck granules**
- Markers of MAPK pathway activation: **cyclin D1 positive and pERK positive**
- Low CD45 expression; Ki-67 index < 10%

OTHER HIGH YIELD POINTS

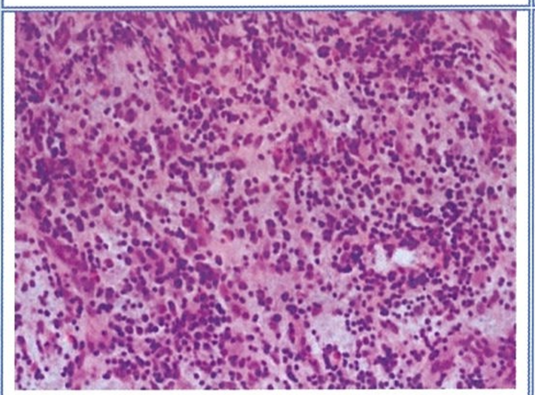


Langerhan cells are positive for CD1a, langerin, S100, CD68 and BRAF V600E (cytoplasmic granular staining)

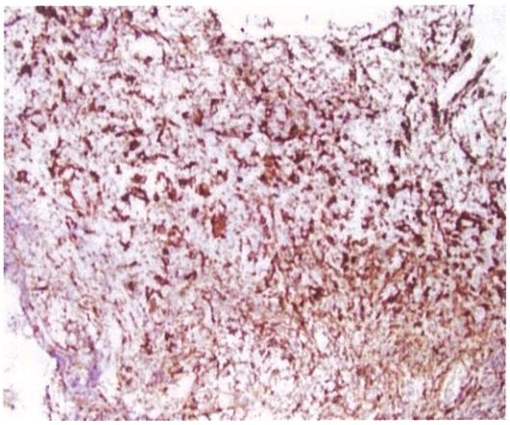
- **MAPK pathway gene mutations in > 85% cases** with **BRAF V600E** being most common **(~50-60%)**, followed by MAP2K1
- Treatment with **BRAF inhibitors (vemurafenib)** in BRAF-mutated cases and **MEK inhibitors** in those harboring MAPK pathway mutations
- CNS LCH presents with neurodegenerative symptoms
- **Multisystem LCH:** ≥ 2 organs and may present with fever, cytopenias, hepatosplenomegaly with jaundice, hyperbilirubinemia, hypoalbuminemia
- Common sites: **Bones (commonly craniofacial, femur, spine, pelvis, ribs)** presenting as **osteolytic lesions**, skin presenting as nodules or vesicles/bullae/dermatitis in infancy, and pituitary involvement frequently presenting as diabetes insipidus



Axial CT head demonstrating a lytic lesion of the skull with extraosseous extension
Picture courtesy: Jason R. Young, MD



CD163



ALK-POSITIVE HISTIOCYTOSIS

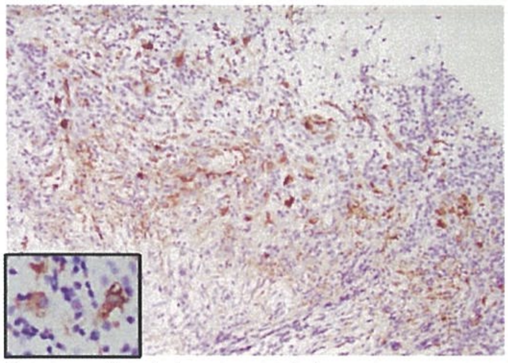
MORPHOLOGY

- **Large oval ("epithelioid"), foamy, and/or spindle cells** in varying proportions without significant nuclear atypia; abundant eosinophilic cytoplasm is present
- The large histiocytes may show irregular nuclear contours (indentation/folding/clefting/lobulation) with fine chromatin and small nucleoli
- Occasional multinucleated cells, including Touton giant cells, may be present
- **Emperipolesis (similar to RDD) may be observed**

OTHER HIGH YIELD POINTS

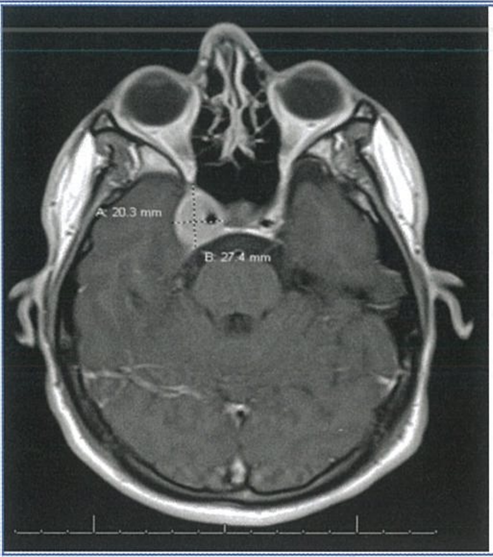
- **Cytoplasmic ALK positivity, occasionally membranous or Golgi-like/dot-like** pattern, but **never a nuclear pattern**
- IHC: **Positive for histiocytic markers** (CD68, CD163, CD14, CD4, and lysozyme) fascin, factor XIIIa; variable expression of S100, cyclin D1, and OCT2
- Negative for CD30, langerin, CD1a
- Ki-67 is low
- **ALK gene fusions**, most commonly **KIF5B-ALK**; other ALK partner genes include CLTC, TPM2, TFG, EML4, DCTN1, COL1A2, TRIM33
- **Targeted therapy with ALK inhibitors** for durable response; favorable prognosis

ALK

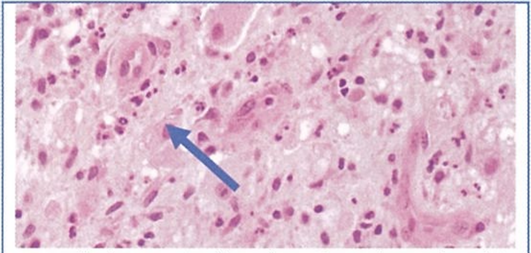


Cavernous sinus lesion composed of CD163-positive histiocytes with cytoplasmic ALK positivity; genetic studies were positive for KIF5B-ALK fusion

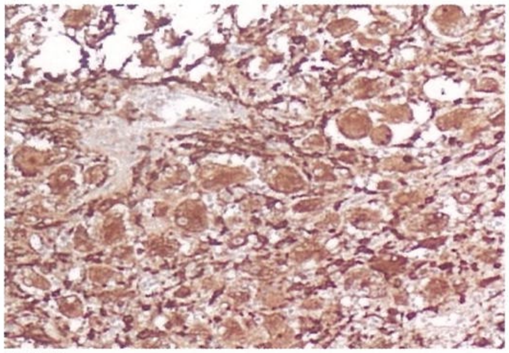
Picture courtesy: Aishwarya Ravindran, MD



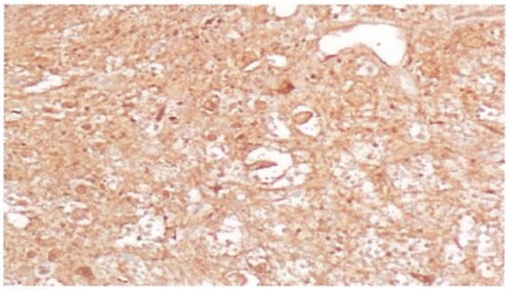
MRI brain in a case of ALK-positive histiocytosis mimicking meningioma: An avidly enhancing mass lesion centered in the right cavernous sinuses with encasement of the right internal carotid artery with minimal extension to the right aspect of sella turcica, radiologically suggestive of a meningioma. The lesion depicted here measures 27 x 20 mm on transverse plane, previously 20 x 28 mm



RDD cells characterized by enlarged round to oval nuclei with small nucleoli and abundant pale eosinophilic cytoplasm with frequent emperipolesis (arrow)



CD163



S100

RDD cells are strongly positive for CD163 and S100 (nuclear and cytoplasmic)

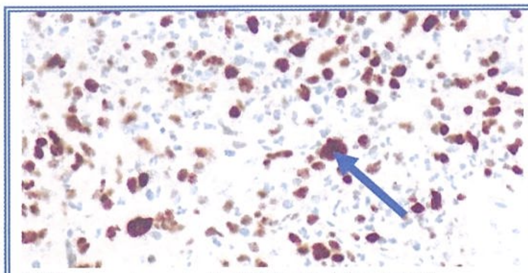
ROSAI-DORFMAN DISEASE

MORPHOLOGY

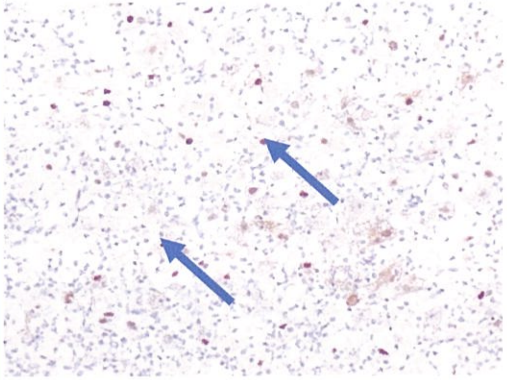
- Characterized by **large histiocytes with round/oval nuclei**, distinct nucleoli, and abundant pale cytoplasm with frequent **engulfment of inflammatory cells (emperipolesis)**
- Abundant plasma cells, small lymphocytes; occasionally, neutrophils may also be present

OTHER HIGH YIELD POINTS

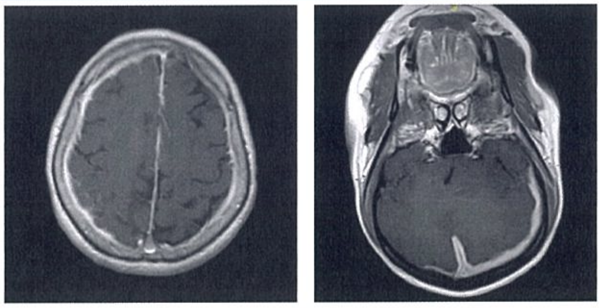
- In some cases, associated stromal fibrosis with inconspicuous emperipolesis and admixed foamy histiocytes make the diagnosis challenging; immunophenotyping **with S100 and OCT2 is helpful in such cases**
- Positive for **CD68**, CD163; ~10% cases can be negative for CD163
- Uniformly **positive for S100 and OCT2**; OCT2 also marks background small B-cells/plasma cells, which serve as an internal control for evaluating OCT2 expression in RDD histiocytes
- Frequently positive for **p-ERK and cyclin D1**
- **BRAF V600E rarely positive**; these cases require evaluation for a **mixed histiocytosis** (ECD+RDD, RDD+LCH)
- Negative for CD1a, langerin, ALK
- Frequent **mimicker of meningioma when it involves the dura**
- B symptoms (fever, night sweats, unintentional weight loss) may be present in 1/3 of cases
- **MAPK pathway alteration**, with the most common being **KRAS, NRAS, MAP2K1, ARAF, and CSF1R** gene mutations; BRAF V600E is extremely rare
- Suspected familial cases should be evaluated for **SLC29A3 and TNFRSF6 germline mutations**
- **Overall good prognosis**; surgery for easily resectable mass/mass-like lesions
- Persistent/recurrent disease could be treated with **MEK inhibitors**



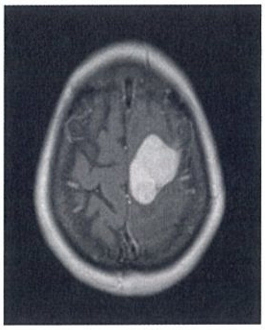
OCT2 strongly marks the RDD cells (blue arrow). Background small B-cells and plasma cells are also positive for OCT2 and serve as an internal control



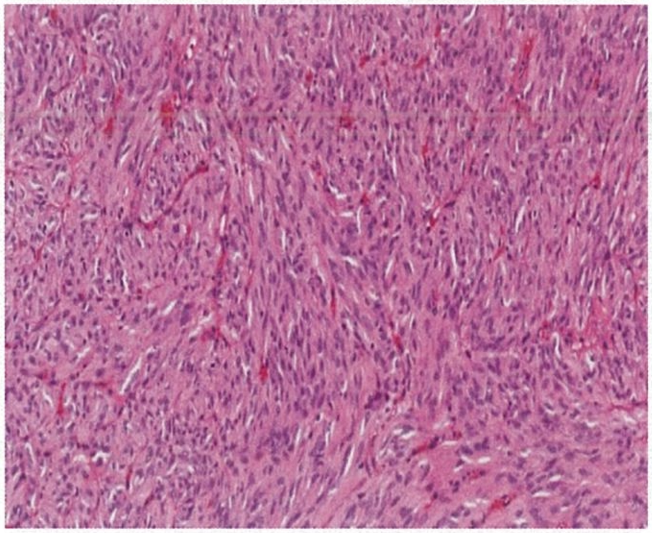
RDD cells are uniformly positive for cyclin D1 (strong nuclear and weak cytoplasmic)



MRI brain with contrast-demonstrated dural lesions suggestive of meningiomatosis; RDD is a mimicker of meningioma when it involves the dura
Picture courtesy: Jason R. Young, MD



T2-weighted MRI brain depicting a large dural lesion with mass effect on the adjacent brain
Picture courtesy: Jason R. Young, MD

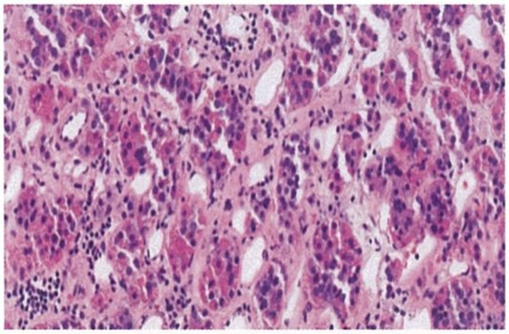


SELLAR TUMORS

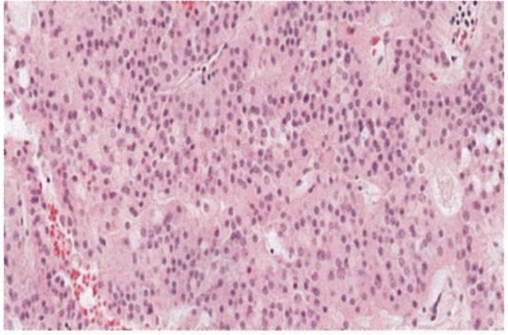
LOPA MODI, MD

18. SELLAR TUMORS

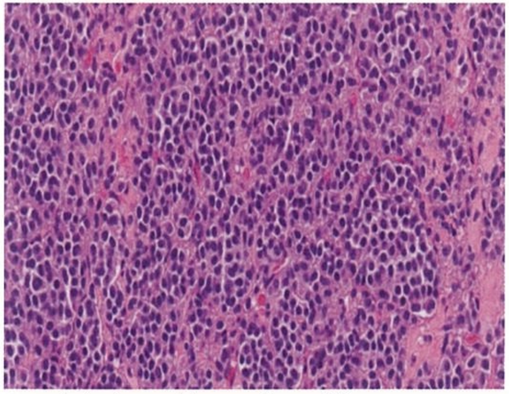
PITUITARY ADENOMA



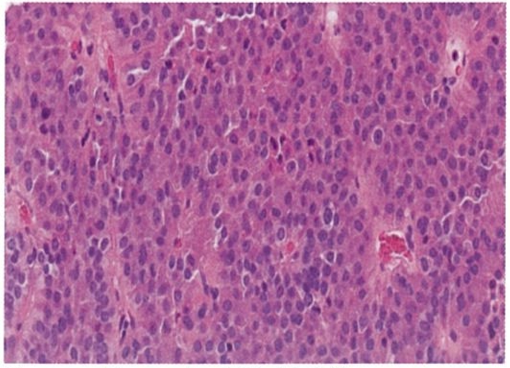
Normal pituitary. Mixture of cells, small acini



Diffuse growth (chromophobe)



Expanded acinar architecture (basophil)



Monomorphic, round nuclei (acidophil)

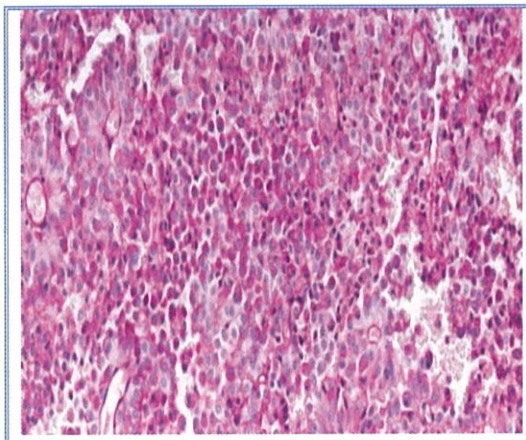
PITUITARY ADENOMA/PITUITARY NEUROENDOCRINE TUMOR (PitNET)

MORPHOLOGY

- Location
  - Sellar region with/without suprasellar extension
  - Ectopic: Sphenoid sinus > clival, suprasellar
  - Rarely arises in teratoma
- Monomorphic neuroendocrine cells: Round nuclei, speckled chromatin (salt and pepper), no conspicuous nucleoli
- Cells can be acidophilic, basophilic, or chromophobic (nonspecific)
- Variety of histologic patterns: Diffuse, papillary, trabecular
- Touch prep: Cellular, discohesive, homogeneous neuroendocrine cell population
- Reticulin stain highlights expanded acinar architecture
- Crooke cell adenoma: Abundant accumulation of pale hyaline material in cytoplasm; mostly ACTH producing, highlighted with cytokeratin
- Hemorrhagic necrosis can be seen in large tumors (pituitary apoplexy)

OTHER HIGH YIELD POINTS

- Most common tumor of the sellar region
- Benign but can invade adjacent structures
- IHC: (+) synaptophysin, chromogranin; (-) S100
- Increased propensity for early recurrence and resistance to therapy
  - Sparsely granulated somatotroph
  - Silent corticotroph
  - Crooke cell
  - Plurihormonal PIT1 positive
  - Lactotroph in men
- Clinical
  - Hormone excess syndrome (hyperprolactinemia, Cushing disease, etc.) – frequently microadenoma
    - Prolactin may be elevated secondary to "stalk effect" rather than tumor production
  - Incidental – most frequently macroadenoma
  - Symptoms of intracranial mass effect
  - "Pituitary apoplexy" secondary to acute hemorrhagic necrosis
- Imaging
  - MRI shows a sellar/suprasellar mass with or without compression of optic chiasm
  - Cavernous sinus or sphenoid sinus invasion may or may not be present
  - T1-weighted image: Hypointense mass
  - T2-weighted image: Hypointense or hyperintense mass
- Genetic factors
  - Majority are sporadic
  - Somatotroph adenomas: Somatic mutation in GNAS
  - Corticotroph adenomas: Mutations in USP48, NR3C1, and CABLES1
  - Pituitary carcinoma: TP53 (not diagnostic of carcinoma)
- Classification
  - Transcription factor expression (PIT1, TPIT/TBX19, SF1) – nuclear staining
    - Lactotroph (PIT1-lineage): Most common (~50% of adenomas); prolactin → galactorrhea and amenorrhea (females) or sexual dysfunction (males)
    - Somatotroph (PIT1-lineage): GH → gigantism/acromegaly
    - Thyrotroph (PIT1-lineage): (Rare) TSH → hyperthyroidism
    - Corticotroph (TPIT-lineage): ACTH → excessive cortisol, Cushing disease
    - Gonadotroph (SF1-lineage): FSH, LH, and/or alpha-subunit → menstrual disturbances in females or sexual dysfunction in males
    - Null cell (lacks distinct lineage): Does not produce hormones
    - Plurihormonal: Multiple hormones


Crooke cell adenoma (hyalinized)

Path Presenter

- Hormone secretion – cytoplasmic staining; may have high background
  - Functioning adenomas secrete hormones and cause symptoms related to hormone secretion
  - Silent adenomas are IHC positive but do not secrete hormone
  - Non-functioning adenomas do not secrete hormones; symptoms related to mass effect (bitemporal hemianopsia, diplopia, headache)
- Cytokeratin (CAM 5.2) staining pattern
  - Most useful for somatotroph and corticotroph tumors
  - Somatotroph
    - Perinuclear → densely granulated
    - Fibrous bodies → sparsely granulated
  - Corticotroph
    - Strong → densely granulated
    - Variable → sparsely granulated
    - Intense ring-like perinuclear staining → Crooke cell tumor
- Pituitary carcinoma
  - Diagnosis requires craniospinal dissemination and/or systemic metastasis
  - Predictive markers of malignant progression not well established

PITUITARY BLASTOMA

PITUITARY BLASTOMA

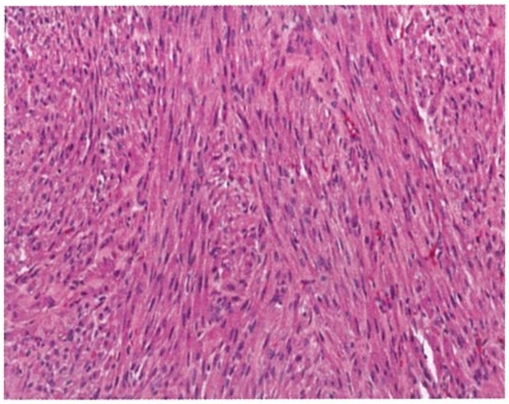
MORPHOLOGY

- Embryonal neoplasm of sellar region
- 3 components:
  - Primitive blastemal cells – small, chromophobic, and undifferentiated
  - Neuroendocrine cells – round nuclei and abundant cytoplasm arranged in lobules or sheets
  - Rathke's pouch epithelium – cuboidal to columnar cells forming gland-like structures

OTHER HIGH YIELD POINTS

- Extremely rare, occurs in infants
- Commonly presents with Cushing syndrome due to elevated ACTH
- Associated with germline and somatic DICER1 mutations
- IHC: (+) ACTH; high Ki-67

POSTERIOR PITUITARY TUMORS


Spindled cells in intersecting fascicles

SPINDLE CELL ONCOCYTOMA

MORPHOLOGY

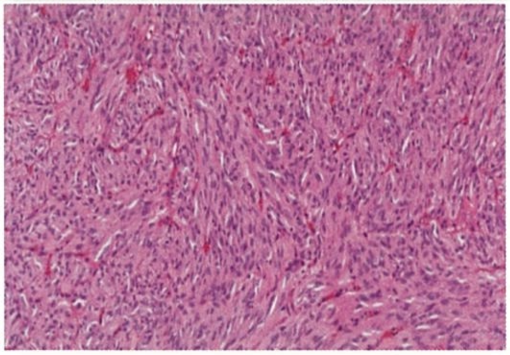
- **Spindled to epithelioid oncocytic** non-neuroendocrine neoplasm
- **Intersecting fascicles and poorly defined nodules**
- **Variable nuclear pleomorphism**

OTHER HIGH YIELD POINTS

- Rare, primarily adults
- IHC: **(+) TTF1, S100, EMA**
- Good prognosis but higher rate of recurrence compared to pituicytoma and granular cell tumor of the sellar region

18. SELLAR TUMORS

Storiform pattern with bland bipolar spindle cells



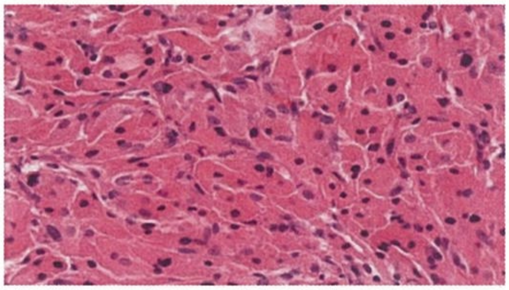
PITUICYTOMA

MORPHOLOGY

- Low-grade glial tumor composed of bland bipolar spindle cells arranged in a fascicular or storiform pattern
- Fibrillary background
- Circumscribed, solid
- Lacks Rosenthal fibers, eosinophilic granular bodies, hyalinized blood vessels

OTHER HIGH YIELD POINTS

- Rare, primarily adults
- IHC: (+) TTF1, S100; (+/-) GFAP; (-) synaptophysin
- Good prognosis
- Likely on a spectrum with other posterior pituitary tumors (granular cell tumor of the sellar region and spindle cell oncocytoma]



Abundant granular eosinophilic cytoplasm

GRANULAR CELL TUMOR OF THE SELLAR REGION

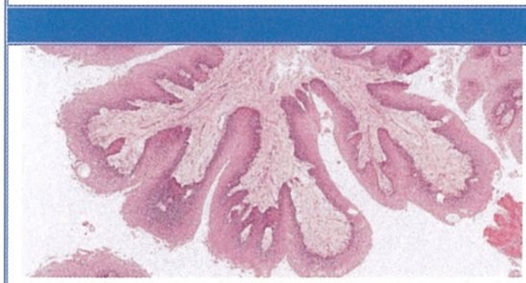
MORPHOLOGY

- Densely packed polygonal cells with abundant **granular eosinophilic cytoplasm** (lysosomes: positive for PAS, diastase resistant)
- **Perivascular lymphocytes**

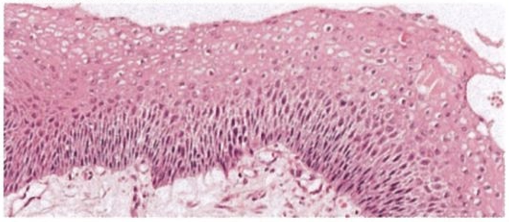
OTHER HIGH YIELD POINTS

- Rare, primarily adults
- IHC: **(+) TTF1, CD68; (+/-) S100**
- Slow progression and benign clinical course

CRANIOPHARYNGIOMAS



Papillary architecture



Non-keratinizing squamous epithelium

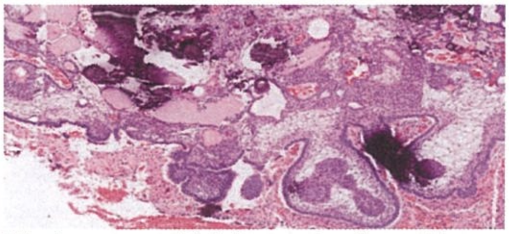
PAPILLARY CRANIOPHARYNGIOMA (CNS WHO GRADE 1)

MORPHOLOGY

- Resembles a squamous papilloma: non-keratinizing epithelium with fibrovascular cores
- Solid sheets
- Thought to arise from elements related to Rathke's pouch
- Lacks stellate reticulum, "wet" keratin, calcifications
- Well demarcated tumor-brain interface
- **Typically solid or mixed solid/cystic tumors; rarely purely cystic**

OTHER HIGH YIELD POINTS

- Exclusively in adults
- IHC: (+) BRAF V600E mutation antibody, p63
- Molecular: BRAF V600E mutation
- Malignant progression is extremely rare



Mixed squamous epithelial tumor - basal layer with palisading, stellate reticulum, calcifications

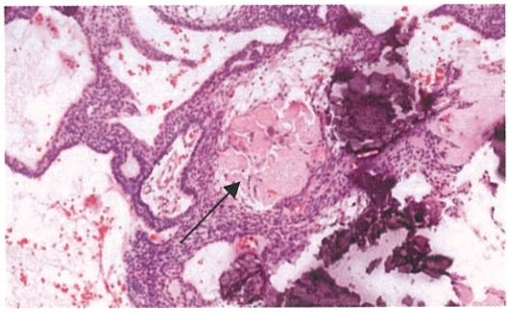
ADAMANTINOMATOUS CRANIOPHARYNGIOMA (CNS WHO GRADE 1)

MORPHOLOGY

- Mixed solid and cystic squamous epithelial tumor
- Basal layer with palisading
- Stellate reticulum (loose background)
- "Wet" keratin, calcifications, cholesterol clefts, xanthogranulomatous reaction
- Gross: "Machine oil" cyst fluid

OTHER HIGH YIELD POINTS

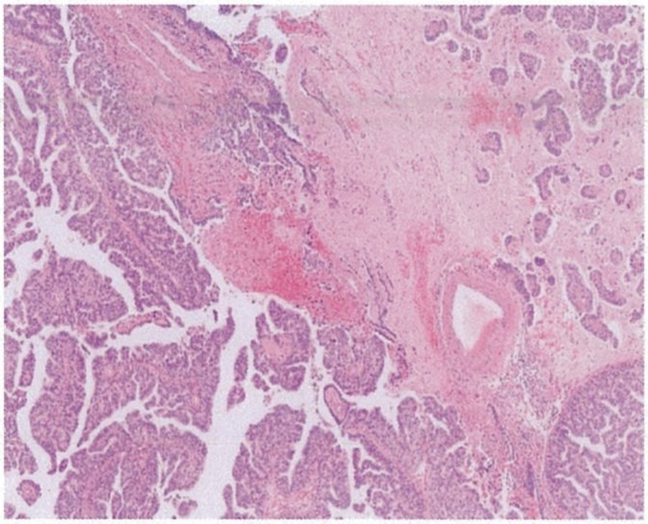
- Bimodal age distribution (1st and 5th decades)
- **Adamantinomatous variant represents almost all craniopharyngiomas in children and ~80% of craniopharyngiomas in adults**
- Thought to arise from elements related to Rathke's pouch
- IHC: Nuclear expression of beta catenin; (+) p63



"Wet" keratin

- Molecular: **Activating CTNNB1 mutations** (encodes beta catenin)
- Malignant progression is extremely rare
- Location: **Majority have suprasellar component**; can extend into the anterior, middle, or posterior cranial fossa
- Clinical presentation: Visual impairment and endocrine deficits; **rarely incidental** (< 2% of cases)

Path Presenter

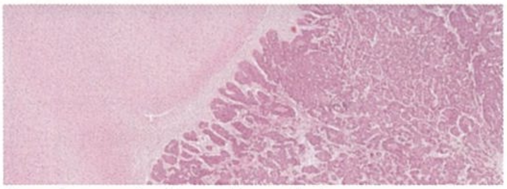


CNS METASTASIS

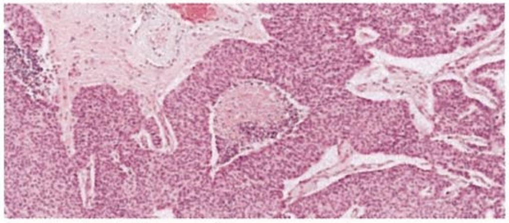
RAQUEL T. YOKODA, MD

19. CNS METASTASIS

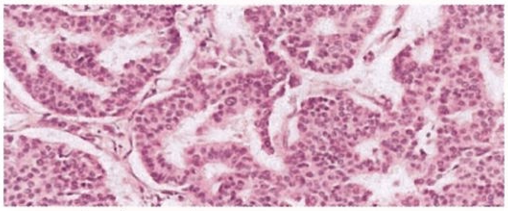
CNS METASTASIS



Clear demarcation from adjacent brain



Reactive brain tissue and tumor necrosis



Metastatic adenocarcinoma

OVERVIEW

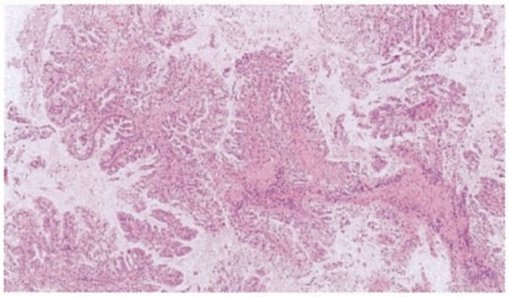
MORPHOLOGY

- Histomorphology and immunophenotype generally match primary tumor
- Well circumscribed and **clearly demarcated** from adjacent brain
- Occasionally, metastatic small cell neoplasms, lymphomas, and melanomas show infiltrative growth patterns
- **Tumor necrosis** can be extensive

OTHER HIGH YIELD POINTS

- **Most common CNS malignancy in adults**
- Most common sites of origin:
  - Men: 1) lung, 2) gastrointestinal, 3) melanoma, 4) kidney
  - Women: 1) lung, 2) breast, 3) gastrointestinal, 4) melanoma
  - Children: 1) leukemia/lymphoma, 2) germ cell tumors, 3) osteosarcoma, 4) neuroblastoma
- Usually multiple, well-circumscribed lesions
- Majority (80%) in cerebral hemispheres (especially at arterial border zones, gray-white junction)
- Metastases to dura, leptomeninges, and sellar region also occur
- Metastatic melanomas can show extensive hemorrhage

Path Presenter   Path Presenter



Metastatic adenocarcinoma, lung primary, with mucinous papillary morphology

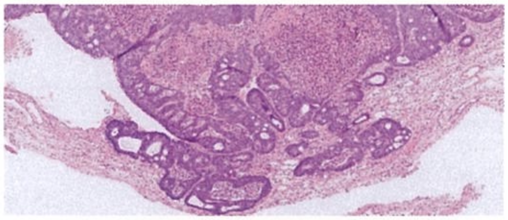
METASTATIC LUNG CARCINOMA

MORPHOLOGY

- May be adenocarcinoma or squamous carcinoma
- Can have solid, papillary, or other architectures
- Can present poorly differentiated and discohesive (NUT carcinoma of the lung and SMARCA4-deficient variants)

OTHER HIGH YIELD POINTS

- **Most common** metastatic tumor to the brain
- PD-L1 immunohistochemistry and DNA sequencing (for targetable mutations) advised regardless of reported status in primary
- Leptomeningeal spread in EGFR-amplified tumors alters EGFR inhibitor dosing



Metastatic colon cancer with leptomeningeal involvement

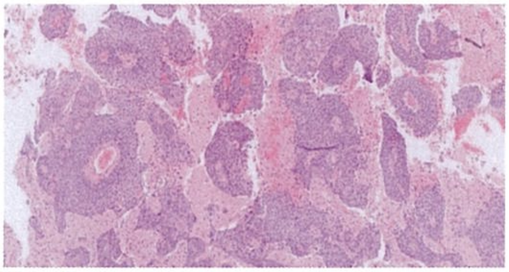
METASTATIC COLON CARCINOMA

MORPHOLOGY

- Glandular epithelium with **dirty necrosis** (necrotic debris intermixed with neutrophils in lumen)

OTHER HIGH YIELD POINTS

- Leptomeningeal spread may require more aggressive therapy (e.g., intrathecal chemotherapy)



Metastatic squamous cell carcinoma

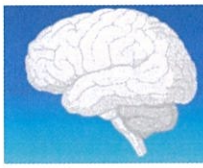
METASTATIC SQUAMOUS CELL CARCINOMA

MORPHOLOGY

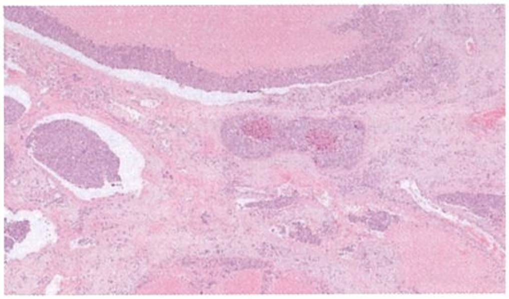
- Squamous differentiation with polygonal cells and intercellular bridges
- May show angiocentric growth pattern (hematogenous spread)

OTHER HIGH YIELD POINTS

- Usually from lung primary, can also come from head and neck
- If oropharyngeal primary, p16 can help define mode of treatment (HPV-related SCC of oropharynx responds well to radiation)



19. CNS METASTASIS



Metastatic breast carcinoma

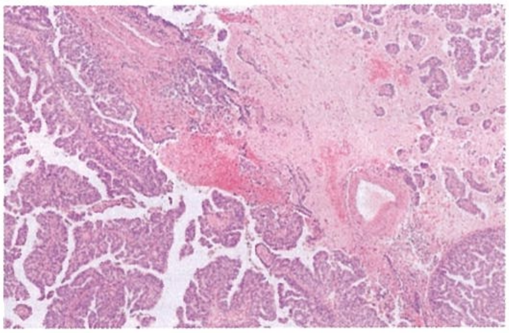
METASTATIC BREAST CARCINOMA

MORPHOLOGY

- May show ductal or lobular architecture
- Frequently shows comedo necrosis

OTHER HIGH YIELD POINTS

- ER/PR/HER2 status required for all metastatic lesions regardless of status in primary
- PD-L1 immunohistochemistry reported as combined positive score (CPS)
- CPS includes tumor and immune cells
- CPS > 10 is threshold for checkpoint inhibitor therapy
- Triple-negative tumors can be negative for GATA3 as well
- SOX10 is positive in a subset of triple-negative tumors
- For triple-negative, GATA3-negative, SOX10-positive, poorly differentiated metastases, need negative melanoma markers to conclude breast origin



Metastatic urothelial carcinoma

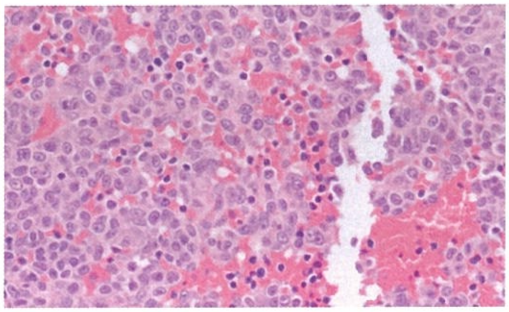
METASTATIC UROTHELIAL CARCINOMA

MORPHOLOGY

- May show solid, papillary, or other architectures

OTHER HIGH YIELD POINTS

- Early and most common mutation is in TERT promoter
- RB1, FGFR alterations also common
- Papillary variants can have HER2/ERBB2 amplification
- PD-L1 expression, tumor mutational burden, and mismatch repair deficiency are used to predict response to checkpoint inhibitors



Metastatic melanoma

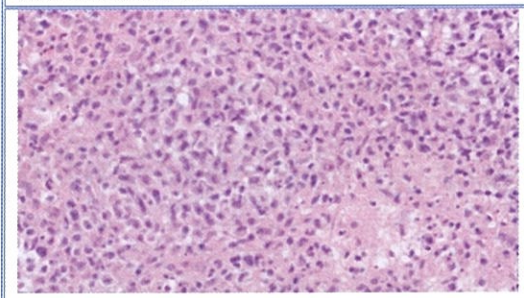
METASTATIC MELANOMA

MORPHOLOGY

- May show solid or discohesive architecture
- Frequently shows extensive **hemorrhage**
- Frequently shows prominent nucleoli
- May be with or without pigment
- May be incidental finding in hemorrhagic specimen

OTHER HIGH YIELD POINTS

- BRAF V600E immunostain can be helpful



Atypical lymphoid infiltrate

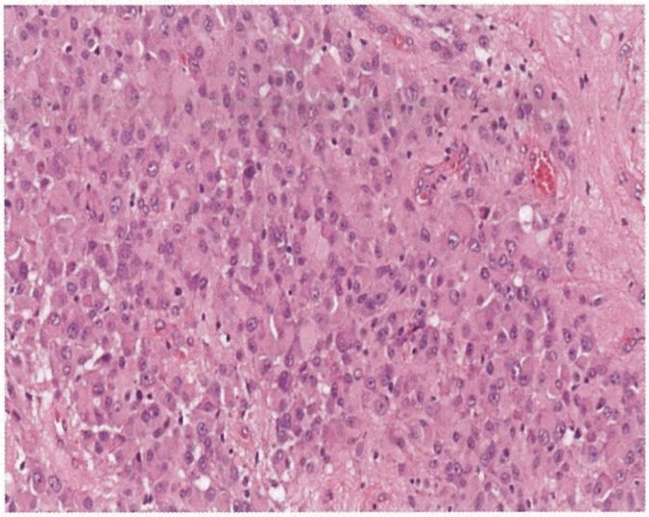
METASTATIC CNS LYMPHOMA

MORPHOLOGY

- Medium to large lymphoid cells with irregular nuclear contours
- Diffuse or angiocentric growth patterns are common
- **Diffuse large B-cell lymphoma (DLBCL)** most common metastatic lymphoma to CNS (CD20, PAX5, BCL2, MUM1)

OTHER HIGH YIELD POINTS

- DLBCL is the most common primary (and metastatic) lymphoma of CNS
- Frequently EBV positive (do EBER) if history of immunodeficiency
- Imaging and clinical history distinguish primary vs. secondary CNS involvement



TUMOR SYNDROMES

STEVEN N. SCHWARTZ, MD

20. TUMOR SYNDROMES

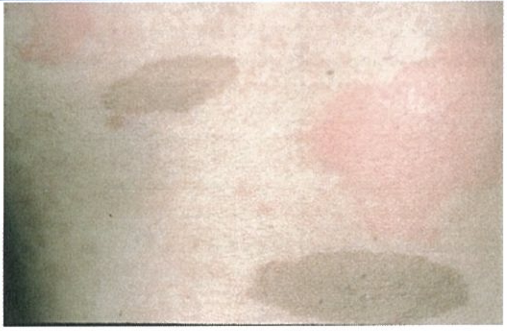
TUMOR SYNDROMES

SUMMARY OF TUMOR SYNDROMES

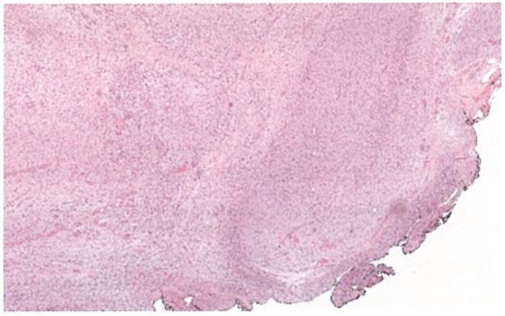
	Inheritance and Genetics	Nervous System Manifestations	Cutaneous Manifestations	Other Manifestations
Neurofibromatosis Type 1	Autosomal dominant *NF1*, chromosome 17	Neurofibromas, MPNST, optic nerve glioma, pilocytic or diffuse astrocytoma	Café-au-lait macules, axillary and inguinal freckling	Iris hamartomas, osseous lesions, pheochromocytoma, gastrointestinal stromal tumor, juvenile myelomonocytic leukemia, juvenile xanthogranuloma, melanoma, duodenal carcinoid, and medullary thyroid carcinoma
Neurofibromatosis Type 2	Autosomal dominant *NF2*, chromosome 22	Bilateral vestibular schwannomas, non-vestibular schwannomas, meningioma, meningioangiomatosis, spinal ependymoma, glial microhamartomas and cerebral calcifications	Café-au-lait macules (rare)	Posterior lens opacities and retinal hamartomas
Tuberous Sclerosis	Autosomal dominant *TSC1*, chromosome 9 *TSC2*, chromosome 16	Cortical hamartomas (tubers), subependymal nodules, subependymal giant cell astrocytoma and radial glioneuronal heterotopias	Facial angiofibroma, hypomelanotic macules, shagreen patches and subungual fibromas	Retinal hamartoma, cardiac rhabdomyoma, adenomatous polyps of the intestine, cysts of the lung and kidney, lymphangioleiomyomatosis, renal angiomyolipoma, bone cysts, dental enamel pits, gingival fibromas and chordoma
Von-Hippel Lindau Disease	Autosomal dominant *VHL*, chromosome 3	Hemangioblastoma	None	Retinal hemangioblastoma, clear cell renal cell carcinoma, pheochromocytoma, pancreatic serous cystadenoma and neuroendocrine tumor, visceral cysts, endolymphatic sac tumor and papillary cystadenoma of epididymis and broad ligament
Cowden Syndrome	Autosomal dominant *PTEN*, chromosome 10	Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos disease), megalencephaly and ganglioneuromas	Facial trichilemmoma and acral keratosis	Hamartomatous intestinal polyps, follicular carcinoma and other thyroid lesions, breast carcinoma and endometrial carcinoma
Turcot Syndrome	CMMRD: Autosomal recessive HNPCC: Autosomal dominant *MLH1*, chromosome 3 *MSH2*, chromosome 2 *MSH6*, chromosome 2 *PMS2*, chromosome 7 FAP: Autosomal dominant	CMMRD: Glioblastoma HNPCC: Glioblastoma FAP: Medulloblastoma (WNT-activated)	CMMRD: Café-au-lait macules HNPCC: Sebaceous adenomas and carcinomas FAP: Epidermal inclusion cysts	CMMRD: Hematologic malignancy (predominantly T-cell lymphoma), adenomatous intestinal polyps and colorectal carcinoma HNPCC: Adenomatous intestinal polyps, colorectal carcinoma, endometrial

	APC, chromosome 5			carcinoma, upper urothelial tract carcinoma, gastric carcinoma and hepatobiliary carcinoma FAP: Adenomatous intestinal polyps, colorectal carcinoma, desmoid fibromatosis, lipomas, osteoma, thyroid carcinoma and hepatoblastoma
Li-Fraumeni Syndrome	Autosomal dominant *TP53*, chromosome 17	Glioblastoma, medulloblastoma and choroid plexus carcinoma	None	Breast carcinoma, bone and soft tissue sarcomas, adrenocortical carcinoma, leukemia and Wilms tumor
Gorlin Syndrome	Autosomal dominant *PTCH1*, chromosome 9 *SUFU*, chromosome 10	Medulloblastoma (SHH-activated), calcification of falx cerebri, meningioma	Basal cell carcinoma, palmar and plantar pits	Odontogenic keratocyst, cardiac and ovarian fibromas and skeletal abnormalities
Retinoblastoma	Autosomal dominant *RB1*, chromosome 13	Pineoblastoma	None	Retinoblastoma, osteosarcoma and secondary radiation-induced malignancy

NEUROFIBROMATOSIS TYPE 1



Cafe-au-lait macules in patient with NF1



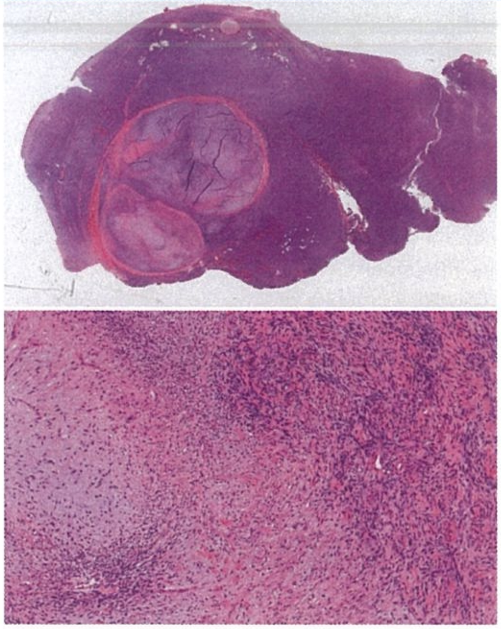
Plexiform neurofibroma

MORPHOLOGY

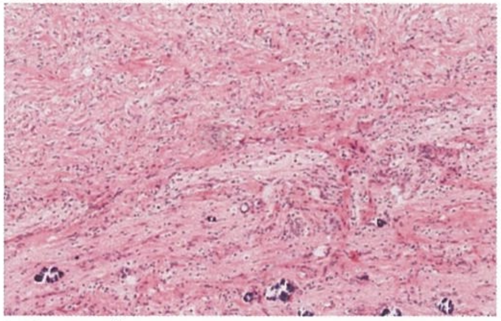
- Most NF1-associated neurofibromas are similar to sporadic ones
- **Plexiform neurofibromas demonstrate rope-like expansions of multiple nerve fascicles ("bag of worms")**
    - ➢ Malignant transformation to MPNST is possible
    - ➢ Appears more fleshy, heterogeneous and invasive
    - ➢ Often has foci of necrosis, hemorrhage, and chalky calcifications
- Higher incidence of MPNST
- Optic gliomas typically have classic appearance of pilocytic astrocytomas
    - ➢ Greater likelihood of invading optic nerve parenchyma and overlying leptomeninges
    - ➢ Can secondarily induce meningothelial hyperplasia
    - ➢ Often stop growing or regress without treatment
    - ➢ Most of these are not biopsied
- NF1 is also associated with pilocytic astrocytoma of the cerebellum and brainstem
    - ➢ Brainstem pilocytic astrocytomas are indolent, though many appear infiltrative on histology
- Increased risk of malignant gliomas
    - ➢ Most often encountered in adults with cerebral masses
    - ➢ Diffuse higher-grade astrocytomas; more histologically diverse, can be difficult to classify
    - ➢ Can have component resembling conventional pilocytic astrocytoma in an otherwise high-grade astrocytoma

OTHER HIGH-YIELD POINTS

- Variable clinical presentations and severity
    - ➢ Depends on age and degree of penetrance
- Also known as peripheral neurofibromatosis or von Recklinghausen disease
- Estimated incidence 1 in 3,000
- Autosomal dominant, though half of cases are sporadic
    - ➢ *NF1* gene on chromosome 17



MPNST arising in a plexiform neurofibroma



Optic nerve glioma

- Definitive diagnosis requires at least two of:
    - Six café-au-lait macules
    - Axillary or groin freckling
    - More than one plexiform or more than two non-plexiform neurofibromas
    - Optic glioma (pilocytic astrocytoma)
    - More than two Lisch nodules (iris hamartomas)
    - Dysplasia/absence of sphenoid bone or dysplasia/thinning of long bone cortex
    - NF1 in a first-degree relative
- Presence of paraspinal intraneural neurofibromas, especially multiple, is essentially diagnostic of NF1
- Plexiform neurofibromas and massive diffuse-appearing soft tissue neurofibromas are largely only seen in NF1
- NF1-associated diffuse astrocytic neoplasms frequently show ATRX loss and p53 overexpression but lack of IDH1 R132H immunoreactivity

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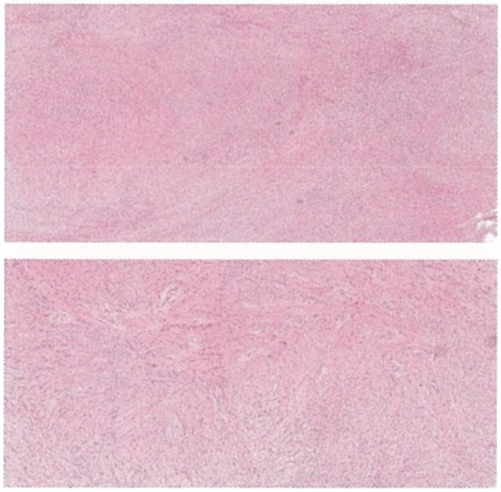
NEUROFIBROMATOSIS TYPE 2

Schwannoma



MORPHOLOGY

- **Vestibular schwannomas in NF2 are more likely to be multicentric and have a multinodular or "cluster of grapes" appearance**
    - Also have a slightly higher proliferative index and are more likely to invade the nerve
- Plexiform schwannomas of the skin or head and neck region can be associated with NF2
    - Often mistaken for plexiform neurofibromas
- **Meningiomas are the second most common tumor type in** NF2
    - Particularly in NF2 patients, schwannomas and fibrous/transitional meningiomas can look very similar
    - Some suggestion of increased frequency of higher-grade meningiomas
- **Meningioangiomatosis** is a plaque-like mass of the cortex or leptomeninges
    - Characterized by variably cellular meningothelial and fibroblastic proliferations in association with a prominent small-vessel vasculopathy
    - Can resemble a vascular malformation, perivascular fibrosis, or meningioma

  - Minimal proliferative activity
  - Reactive and degenerative changes in entrapped or adjacent brain parenchyma are common
  - In NF2, meningioangiomatosis is often multicentric and can be seen in conjunction with glial hamartomas

OTHER HIGH YIELD-POINTS

- Incidence of approximately 1 in 25,000
- Average age of onset: 22 years
- Autosomal dominant
  - *NF2* gene on chromosome 22
- **Pathognomonic finding: bilateral vestibular schwannomas**
  - Aside from bilateral vestibular schwannomas, diagnosis of NF2 can be made with one of: First-degree relative with NF2 plus either one vestibular schwannoma or two of: meningioma, non-vestibular schwannoma, ependymoma, neurofibroma or posterior subcapsular lens opacity
  - Unilateral vestibular schwannoma and two of: meningioma, schwannoma, ependymoma, neurofibroma or posterior subcapsular lens opacity
  - Multiple meningiomas plus one vestibular schwannoma or two of: non-vestibular schwannoma, ependymoma, neurofibroma or cataract
- Up to 40% of children presenting with meningiomas can have NF2
- NF2-associated schwannomas can be distinguished from fibrous meningiomas using immunohistochemistry
  - Schwannomas will be diffusely positive for S100 and SOX10
  - Meningiomas generally show at least focal positivity for EMA and express somatostatin receptor 2A (SSTR2A)

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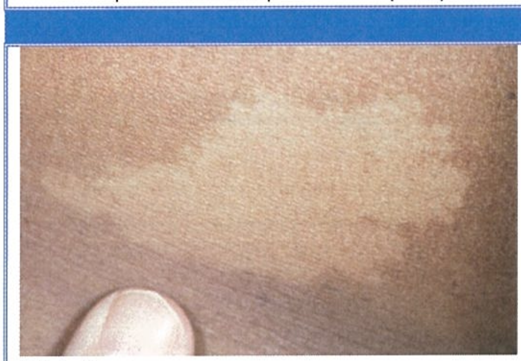
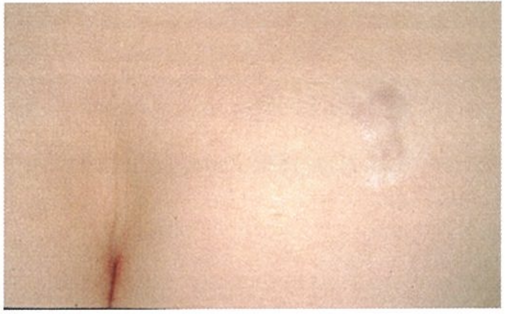
TUBEROUS SCLEROSIS



Ash-leaf spot



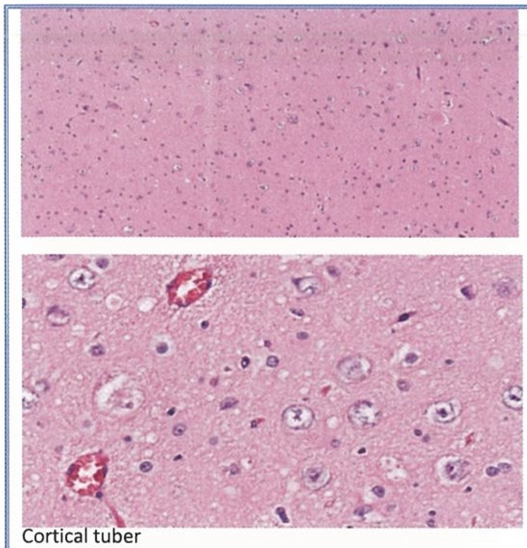
Shagreen patch

MORPHOLOGY

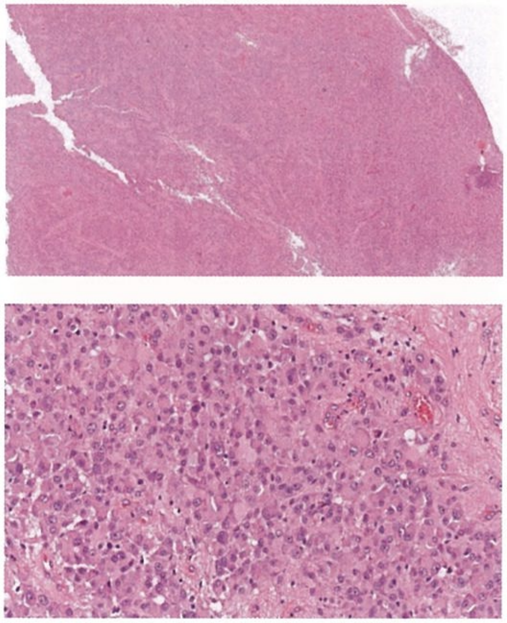
- **Presence of cortical tubers**
  - Protuberant and tan-white
  - Firm or rubbery when large and markedly gliotic
  - Typically associated with blurred gray-white junctions
  - Can be chalky or gritty on cut sections when heavily calcified
  - Composed of enlarged, dysmorphic glioneuronal elements with associated astrocytosis
  - **Most distinctive element is the "balloon cell"** (neuron-like nucleus with eccentrically placed, glassy pink cytoplasm)
  - **Neuronomegaly** is also common
- Radial **glioneuronal heterotopias**
  - Similar gross features to cortical tubers
  - Extend through white matter in a linear or wedge-shaped pattern
  - Histologically features dysplastic glioneuronal cells
- Subependymal nodules
  - Grossly resemble **wax drippings**
  - May be numerous and line the ventricular walls
  - **Can enlarge to form subependymal giant cell astrocytoma (SEGA)**
  - Characterized by atypical, enlarged glioneuronal cells
  - Often have dystrophic calcification
  - Cells can be epithelioid, spindled, or gemistocyte-like
  - Often combine neuron-like nuclei with astrocyte-like cytoplasm
  - Well-demarcated with sharp interfaces with adjacent brain parenchyma
  - Mitotic figures and necrosis are occasionally seen
  - Intratumoral mast cells common and may be numerous

OTHER HIGH YIELD POINTS

- Incidence of approximately 1 in 6,000
- Autosomal dominant
- Germline mutations in:
  - *TSC1* gene on chromosome 9
  - *TSC2* gene on chromosome 16
- Nearly always involves the CNS
- Cutaneous manifestations include:
  - Multiple facial angiofibromas



Cortical tuber



Subependymal giant cell astrocytoma (SEGA)

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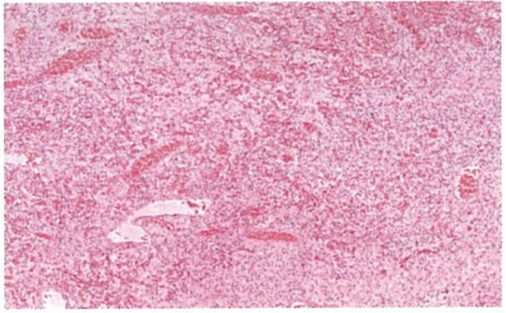
  - Subungual fibromas
  - **Hypomelanotic macules ("ash leaf spots")**
- Other manifestations include:
  - Cardiac rhabdomyomas
  - Pulmonary lymphangioleiomyomatosis
  - Angiomyolipomas of the kidney
  - Renal cysts
- Major diagnostic criteria:
  - Three or more facial angiofibromas
  - Cardiac rhabdomyoma
  - Retinal nodular astroglial hamartomas
  - Cortical tubers
  - Subependymal nodules or SEGA
  - Two or more subungual fibromas
  - Three or more hypomelanotic macules
  - Shagreen patch
  - Lymphangioleiomyomatosis
  - Two or more renal angiomyolipomas
- Minor diagnostic criteria:
  - Dental enamel pits
  - Gingival fibromas
  - Rectal hamartomatous polyps
  - Retinal achromic patches
  - Multiple renal cysts
  - Nonrenal hamartomas
  - "Confetti" skin lesions
- Definite diagnosis requires either two major or one major and one minor criteria
- Possible diagnosis requires either one major or two or more minor criteria
- Cortical tubers are detected on imaging in ~90% of cases
  - About half are calcified
  - Some undergo cystic change
  - In adults, often hypodense to isodense on T1-weighted MRI and hyperintense on T2-weighted MRI
  - In children, this pattern is reversed
- Radial glioneuronal heterotopias have similar imaging characteristics to tubers
- Subependymal nodules have small intraventricular projections
  - Calcifications seen on CT
- SEGA typically >1 cm and enhances with gadolinium on MRI
- Dysplastic cells in TSC lesions often show **variable staining with GFAP**
- Can also be positive for neuronal markers
- Subset of tubers have CD34-immunoreactive cells with highly ramified processes
- SEGAs may show **nuclear TTF-1 positivity**
- Mast cells can be highlighted with c-kit/CD117

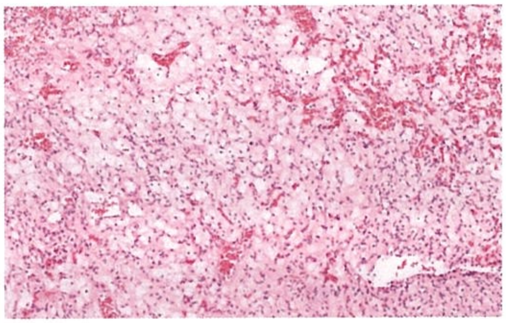
VON-HIPPEL LINDAU DISEASE

MORPHOLOGY

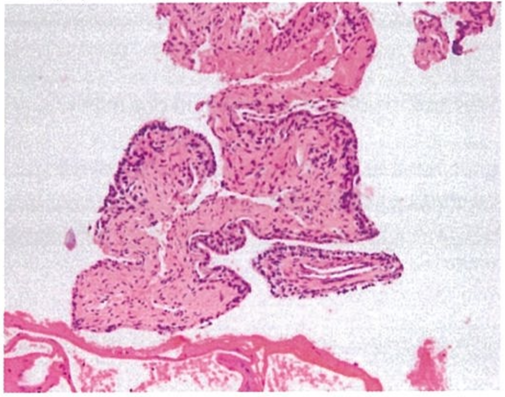
- **Hemangioblastoma,** especially multiple, is a diagnostic hallmark
- ~75% infratentorial, predominantly involving the cerebellum
- Slow-growing tumors with uncertain histogenesis
- Highly vascular tumors with capillary proliferation, fibrosis, and epithelioid stromal cells that appear clear to foamy

Hemangioblastoma

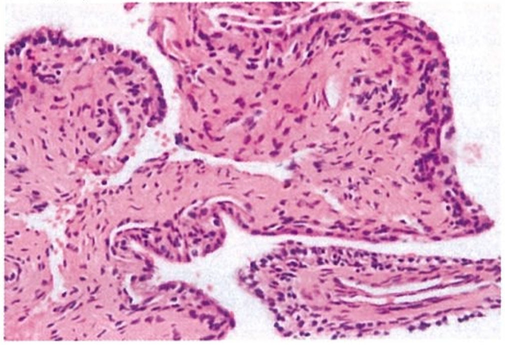




Endolymphatic sac tumor (x10x)



Endolymphatic sac tumor (x20x)



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- Stromal cells can show degenerative nuclear atypia
- Intratumoral mast cells and extramedullary hematopoiesis can be seen
- Adjacent brain parenchyma often shows piloid gliosis
- No distinguishing histologic features between VHL-associated hemangioblastomas and sporadic ones
- Can look like renal cell carcinoma, which also occurs in VHL and frequently metastasizes to the CNS
- **Endolymphatic sac tumor** is a bone-destructive, papillary epithelial tumor
- It shows single layer of bland flattened cuboidal to columnar epithelial cell lining with clear to eosinophilic cytoplasm
- Often focally cystic
- May contain glands or thyroid-like follicles
- Differential diagnosis includes choroid plexus papilloma, middle ear adenoma/adenocarcinoma, middle ear carcinoid, salivary gland choristoma, and metastatic carcinoma

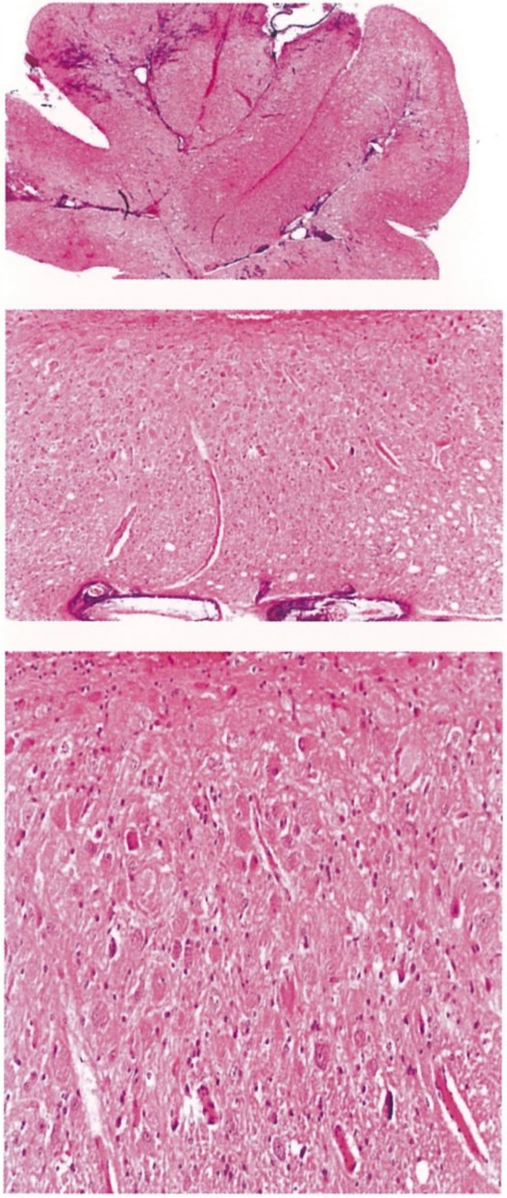
OTHER HIGH YIELD-POINTS

- Incidence approximately 1 in 30,000 to 50,000
- Autosomal dominant
  - *VHL* gene on chromosome 3
- Complex multiorgan disease, which can include:
  - Retinal hemangioblastoma
  - CNS hemangioblastoma
  - Endolymphatic sac tumor
  - Pheochromocytoma
  - Pancreatic cyst or islet tumor
  - Renal cyst
  - Renal cell carcinoma
  - Papillary cystadenoma of the epididymis and uterine broad ligament
- In the presence of a family history, diagnosis requires one of:
  - CNS or retinal hemangioblastoma
  - Renal cell carcinoma
  - Pheochromocytoma
- Without family history, diagnosis requires one of:
  - Multiple hemangioblastomas
  - One hemangioblastoma and another characteristic lesion
- Hemangioblastoma can be distinguished from RCC with immunohistochemistry
  - RCC is positive for cytokeratins and epithelial membrane antigen (EMA)
  - Hemangioblastoma stains with neuron-specific enolase (NSE), GFAP, and S100
- **Inhibin and CD10 can readily distinguish between HB and RCC**
  - Stromal cells of HB almost uniformly stain with inhibin, whereas staining is usually negative in RCC
  - Most RCCs are positive for CD10, whereas HBs are negative
- Endolymphatic sac tumors are typically positive for:
  - Cytokeratins, including CK7 but not CK20
  - EMA
  - S100
  - GFAP
  - NSE

20. TUMOR SYNDROMES

COWDEN SYNDROME

Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum). Note the expansion of the molecular layer, gangliocyte hypertrophy and dysplasia, and vacuolated appearance of the neuropil



Picture courtesy: Dr. Robert E. Schmidt, MD, PhD

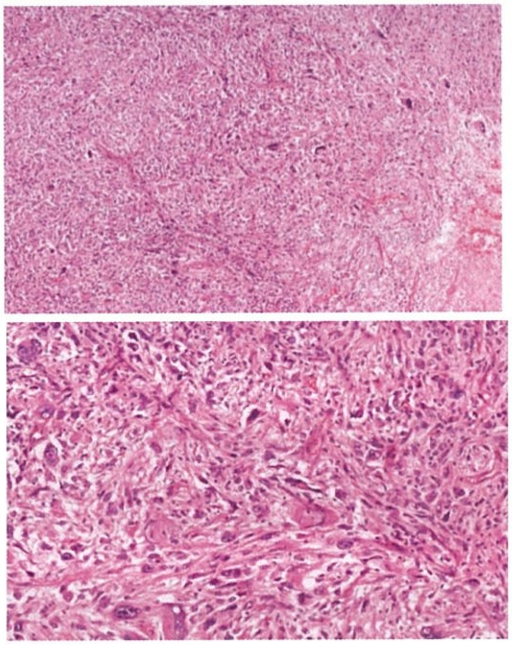
MORPHOLOGY

- Major finding in CNS is Lhermitte-Duclos disease
- Also known as **dysplastic gangliocytoma of the cerebellum**
- Grossly appears white to yellow due to abnormal myelination, may feel firm
- Underlying white matter may be attenuated or cavitated
- **Histologically shows gangliocyte hypertrophy and dysplasia within the internal granular cell layer**
    - Associated expansion of the molecular layer by myelinated axons arising from dysplastic ganglion cells
    - Loss of Purkinje cells
    - Atrophy or cystic degeneration of the underlying white matter
    - Neuropil often appears vacuolated or spongy
    - May be occasional microcalcifications

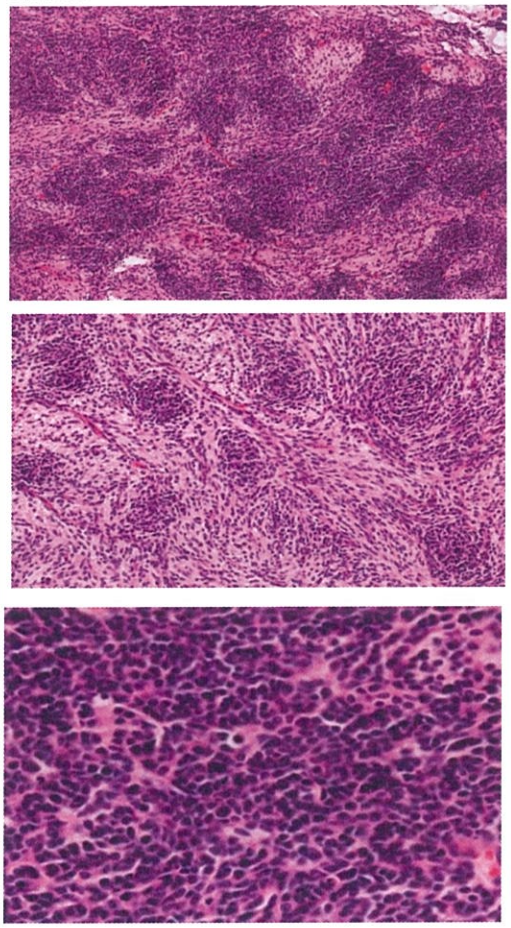
OTHER HIGH YIELD POINTS

- Incidence of approximately 1 in 200,000
- Autosomal dominant
- Inactivating germline mutation in the *PTEN* gene on chromosome 10
- Pathognomonic diagnostic criteria:
    - Adult-onset Lhermitte-Duclos disease (LDD)
    - Mucocutaneous lesions (facial trichilemmoma, acral keratosis, papillomatous papule, mucosal lesions
- Major criteria:
    - Macrocephaly/megalencephaly
    - Breast carcinoma
    - Thyroid carcinoma (especially follicular)
    - Endometrial carcinoma
- Minor criteria:
    - Benign thyroid lesions
    - Decreased IQ
    - Gastrointestinal hamartomas
    - Fibrocystic breast disease
    - Lipomas
    - Renal cell carcinoma or other GU tumors
    - GU malformations
    - Uterine leiomyomas
- In the absence of family history, diagnosis requires one of:
    - Classic mucocutaneous lesions plus two major criteria
    - One major and three minor criteria
    - Four minor criteria
- In the presence of family history, diagnosis requires one of:
    - Classic mucocutaneous lesions
    - One major criterion
    - Two minor criteria
    - History of a related *PTEN* hamartoma syndrome
- LDD appears striated on T2-weighted MRI
    - "Tiger-striped" appearance
- Immunohistochemistry can help diagnose LDD
    - Dysplastic ganglion cells stain positively for synaptophysin, neurofilament, chromogranin, and NeuN

TURCOT SYNDROME



Glioblastoma



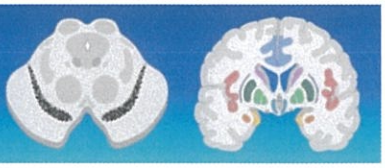
Medulloblastoma

MORPHOLOGY

- Glioblastomas seen in constitutional mismatch repair deficiency syndrome (CMMRD) grossly identical to sporadic counterparts
- Histologically, often display numerous pleomorphic and multinucleated giant cells, but are otherwise identical to their sporadic glioblastomas
- Giant cell variant of glioblastoma may be more common in HNPCC
- Medulloblastomas seen in FAP appear grossly and histologically identical to sporadic counterparts

OTHER HIGH-YIELD POINTS

- Multiple subtypes depending on which mutations are present
- **Autosomal recessive constitutional mismatch repair deficiency syndrome (CMMRD)**
  - ➢ Rare but likely underdiagnosed
- Homozygous germline mutation in the mismatch repair genes (*MSH2*, *MSH6*, *MLH1*, or *PMS2*)
  - ➢ ***PMS2* and *MSH6* are the most common**
- Characterized by:
  - ➢ Café-au-lait macules
  - ➢ Glioblastoma
  - ➢ Hematologic malignancies, particularly T-cell lymphoma
  - ➢ Gastrointestinal polyposis and carcinoma
- Glioblastoma and leukemia/lymphoma typically arise during the first decade of life
- Gastrointestinal polyposis is present by the second decade
- Other reported tumor types include oligodendroglioma, medulloblastoma, urothelial carcinoma, and sarcomas
- **All cancers demonstrate ultra mutated genotype**
- Radiological features of tumors identical to their sporadic counterparts
- Some patients demonstrate agenesis of the corpus callosum and nodular gray matter heterotopias
- Major clinical differential diagnosis for CMMRD is NF1
- Autosomal dominant forms are hereditary nonpolyposis colorectal cancer (HNPCC) syndrome (also known as Lynch syndrome) and familial adenomatous polyposis (FAP)
- HNPCC is caused by heterozygous germline mutations in mismatch repair genes
  - ➢ *MSH2* and *MLH1* are most common
  - ➢ *MSH2* mutations appear to confer a greater risk of gliomas
- Relatively common
  - ➢ Estimated incidence: 1 in 500 to 2,000
- Accounts for approximately 2-5% of colorectal and endometrial cancers, though brain tumors are rare
- Malignant gliomas typically arise during the 3rd or 4th decades of life
- Characterized by colonic polyps (typically <100), with an increased risk of carcinomas of:
  - ➢ Colon
  - ➢ Endometrium
  - ➢ Upper urothelial tract
  - ➢ Stomach
  - ➢ Hepatobiliary tract
- Malignant gliomas, predominantly glioblastomas, are seen
- FAP caused by germline mutation or deletion of *APC* gene on chromosome 5



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- Estimated incidence: 1 in 10,000 to 15,000
- Characterized by innumerable (>100) adenomatous polyps of the colon and other parts of the gastrointestinal tract
- In the CNS, most tumors are medulloblastomas, but astrocytomas, ependymomas, and pineoblastomas have been reported
- Other manifestations include osteomas, desmoid fibromatosis, epidermal inclusion cysts, lipomas, thyroid carcinoma, and hepatoblastoma
- Medulloblastomas seen in FAP are identical to their sporadic counterparts

LI-FRAUMENI SYNDROME

MORPHOLOGY

- Most common CNS tumors are malignant astrocytomas, followed by medulloblastomas and other embryonal neoplasms, choroid plexus carcinomas, and ependymomas
- These tumors appear similar to sporadic counterparts
- Medulloblastomas are often nodular/desmoplastic variants with superimposed severe anaplasia

OTHER HIGH-YIELD POINTS

- Estimated prevalence: 1 in 5,000 to 20,000
- Autosomal dominant
  - Germline mutations in the *TP53* gene on chromosome 17
- Bimodal distribution of CNS tumors
  - First peak during childhood
  - Second peak during 3rd and 4th decades of life
- Most frequent tumor types include:
  - Soft tissue sarcomas
  - Osteosarcoma
  - Breast carcinoma
  - Brain tumors
  - Adrenocortical carcinoma
- Clinical diagnosis requires:
  - Patient younger than 45 years with sarcoma
  - At least one first-degree relative younger than 45 years with any tumor
  - First- or second-degree relative younger than 45 years with cancer or any age with sarcoma
- Tumors often show **strong nuclear immunostaining for p53**

GORLIN SYNDROME

MORPHOLOGY

- Predominant CNS tumor is medulloblastoma
- Histologically appear similar to their sporadic counterparts
- Typically present at an earlier age (average age 2 years versus 7 years for sporadic tumors)

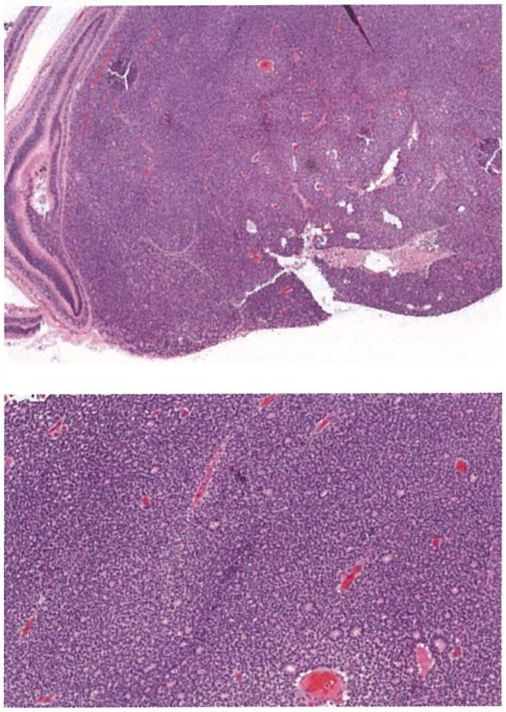
OTHER HIGH YIELD-POINTS

- Also known as **nevoid basal cell carcinoma syndrome (NBCCS)**
- Estimated prevalence: 1 in 57,000 to 164,000
- No gender or ethnicity biases
- Major criteria:
  - First-degree relative with syndrome
  - More than two basal cell carcinomas or one basal cell carcinoma in a patient under 20 years old
  - Medulloblastoma
  - Ovarian fibroma
  - Odontogenic keratocysts
  - More than three palmar or plantar pits
  - Lamellar calcification of falx
  - Developmental rib anomalies
  - Phalangeal flame-shaped radiolucencies
  - Brachymetacarpaly in all four limbs
- Minor criteria:
  - Spina bifida
  - Brachymetacarpaly in at least one limb
  - Hypertelorism or telecanthus
  - Frontal bossing
- Diagnosis requires at least two major criteria or one major and two minor criteria
- Imaging commonly shows falx calcification, sellar bridging, tentorial calcification, abnormal frontal sinus aeration, asymmetrical or dilated ventricles, cavum septum pellucidum, cerebral atrophy, corpus callosum agenesis or dysgenesis, and meningiomas

- Autosomal dominant
- Germline mutations in:
    - *PTCH1* gene on chromosome 9
    - *PTCH2* gene on chromosome 1
    - *SUFU* gene on chromosome 10
- Most mutations lead to truncated proteins

RETINOBLASTOMA

Retinoblastoma



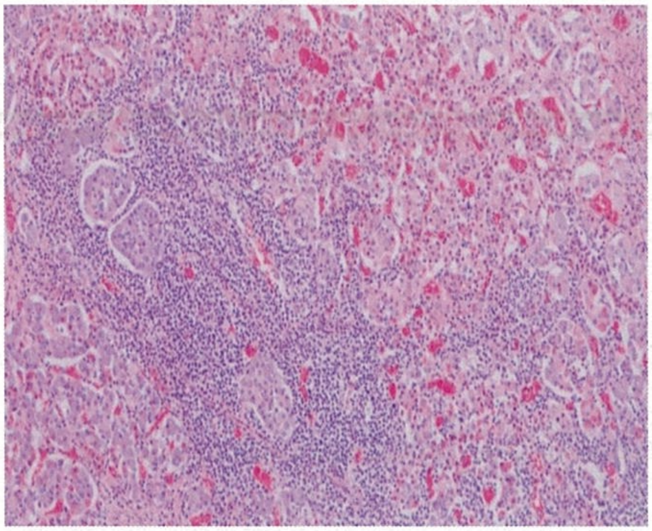
MORPHOLOGY

- Retinoblastoma during early childhood and is often bilateral
- Rare cases also develop pineoblastoma (known as trilateral retinoblastoma)
- Higher rate of developing pineal cysts
- Markedly increased risk of sarcomas, particularly osteosarcoma
- Prone to radiation-induced sarcomas following retinoblastoma therapy

OTHER HIGH YIELD-POINTS

- Caused by an **inactivating germline mutation or deletion of the *RB1* gene on chromosome 13**
- Surveillance brain imaging is recommended until age 5

Path presenter



NON NEOPLASTIC SELLAR PATHOLOGY

EMERY L. PRICE, MD

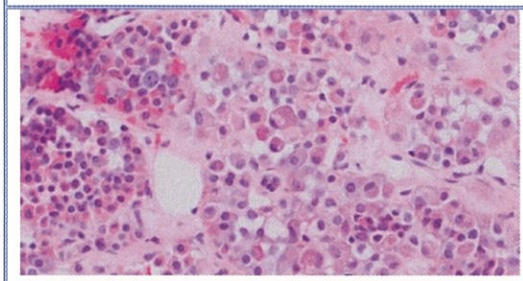
21. NON NEOPLASTIC SELLAR PATHOLOGY

NON-NEOPLASTIC SELLAR PATHOLOGY

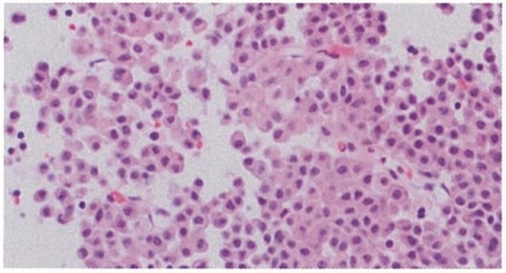
GENERAL OVERVIEW

MORPHOLOGY

- **Glandular epithelial adenohypophysis** is comprised of the anterior pituitary
- **Anterior pituitary**
  - ➢ **Acidophils**
    - ➢ Somatotrophs secrete growth hormone (GH)
    - ➢ Mammotrophs secrete prolocatin (PRL)
  - ➢ **Basophils**
    - ➢ Corticotrophs secrete adrenocorticotrophic hormone (ACTH)
    - ➢ Thyrotrophs secrete thyroid stimulating hormone (TSH)
    - ➢ Gonadotrophs secrete follicle stimulating hormone (FSH) and luteinizing hormone (LH)
  - ➢ Pars intermedia
  - ➢ Pars tuberalis
- **Posterior pituitary (neurohypophysis)**
  - ➢ Characterized by nonsecretory, **nonmyelinated axons**
  - ➢ Secretes antidiuretic hormone (ADH) and oxytocin



Crooke cell change in non-neoplastic pituitary
Picture courtesy: Benjamin B. Cho, MD



Crooke cell change (in Crooke cell adenoma)
Picture courtesy: Benjamin B. Cho, MD

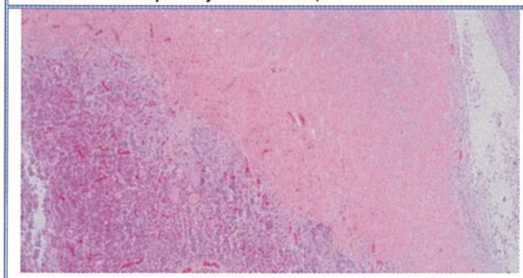
PITUITARY HYPERPLASIA

MORPHOLOGY

- Increase in cell number of 1 or more adenohypophyseal cell types
- **Hyperplasia of a single cell type is more common**
  - ➢ Corticotroph hyperplasia associated with Crooke cell change or Crooke hyaline change
  - ➢ Accumulation of hyaline material in corticotroph cytoplasm
- Reticulin architecture expanded but **remains intact** with uneven pattern of acinar enlargement
- Microscopically may be diffuse or nodular
- Mitotic activity is rare
- Grossly unremarkable with **diffuse enlargement**
- Gland is tan-white and smooth without defined lesion or nodules

OTHER HIGH YIELD POINTS

- Pituitary appears enlarged on radiographic imaging
- Intensity of enlarged pituitary gland similar to gray matter on MRI
- **Most commonly prolactin cell hyperplasia** during pregnancy and lactation
- Corticotroph hyperplasia associated with Crooke cell change common in Cushing Disease



Normal pituitary tissue with adjacent area of pituitary infarction
Picture courtesy: Benjamin B. Cho, MD

PITUITARY APOPLEXY

MORPHOLOGY

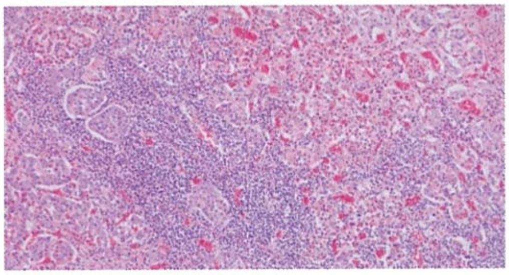
- Histologic findings consistent with ischemia or hemorrhage of the pituitary
- Necrosis will be visualized when the etiology is ischemia
- Gross and microscopic hemorrhage may be present

OTHER HIGH YIELD POINTS

- Presents as hypopituitarism
- **Can be a surgical emergency** if hemorrhage or expansion of tumor results in compression of nearby optic nerve or optic chiasm
- Etiology is varied; therefore, radiologic findings differ
  - ➢ Coagulopathies
  - ➢ Cerebrovascular accidents
  - ➢ Hemorrhagic shock
  - ➢ Traumatic head injury
  - ➢ Heparin therapy
  - ➢ Pre-existing pituitary adenoma
- **"Sheehan syndrome"** in postpartum patients who experienced excessive bleeding during childbirth, leading to pituitary ischemia

21. NON NEOPLASTIC SELLAR PATHOLOGY

INFLAMMATORY DISORDERS OF THE PITUITARY



Lymphocytic hypophysitis
Picture courtesy: Benjamin B. Cho, MD

LYMPHOCYTIC HYPOPHYSITIS

MORPHOLOGY

- Lymphocytic and plasma cell infiltration of the adenohypophysis
- Pituitary architecture may appear replaced by:
  - Lymphocytes (predominantly T-cells)
  - Focal plasma cells and in some cases with few histiocytes
- Chronicity associated with fibrosis
- Lymphoid follicles with well-developed germinal centers can be seen

OTHER HIGH YIELD POINTS

- Rare **autoimmune** process which **can present as hypopituitarism**
- **Most common primary cause of hypophysitis**
- Associated with pregnancy and the postpartum period (F > M incidence)
- Initial presentation can be with headaches or symptoms of mass effect
- Radiologic findings include a symmetrically enlarged anterior pituitary with contrast enhancement

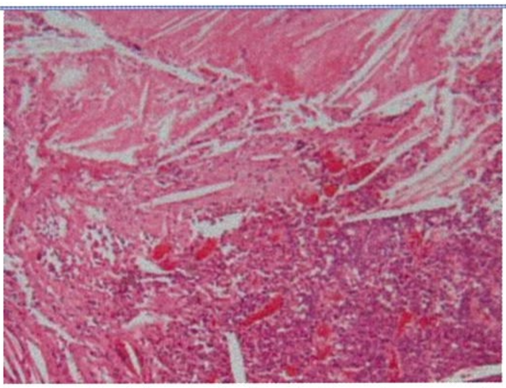
GRANULOMATOUS HYPOPHYSITIS

MORPHOLOGY

- Granulomatous formation within pituitary tissue
- **Abundant histiocytes**
- Occasional multinucleated giant cells
- Lymphoplasmacytic infiltrate
- No organisms seen with special stains

OTHER HIGH YIELD POINTS

- **2nd most common primary hypophysitis**
- Incidence is the same for both sexes
- Mass effect (headache and visual disturbances) with constitutional symptoms (low-grade fever, nausea, vomiting)
- Associated with diabetes insipidus
- MRI may resemble pituitary adenoma with iso- or hypointense signals on T1- and T2-weighted images



Lymphocytes intermixed with pituitary adenoma cells, congested vessels, and cholesterol crystals with xanthomatous reaction and presence of giant cells (multinucleated foreign body type)
Picture courtesy: Martha Tena-Suck, MD

XANTHOMATOUS HYPOPHYSITIS

MORPHOLOGY

- **Foamy histiocytic invasion** of adenohypophysis
- Areas of **central necrosis** may be observed, surrounded by xanthomatous epithelioid cells and foamy cells
- Mixed inflammatory cells (plasma cells and small, mature lymphocytes)

OTHER HIGH YIELD POINTS

- Rarest form of primary hypophysitis
- May clinically mimic a pituitary adenoma
- Symptoms include sequelae of mass effect and endocrine dysfunction
- **CD68 positive**
- **CD1a and S100 negative**

GIANT CELL GRANULOMA OF THE PITUITARY

MORPHOLOGY

- Invasion of the pituitary by noncaseating granulomas
- Occasional **Schaumann bodies**
  - Inclusions of calcium and protein within giant cells of a granuloma
  - Laminated calcifications of the cytoplasm

OTHER HIGH YIELD POINTS

- Incidence is equal in both sexes

SECONDARY INFLAMMATORY DISORDERS OF THE PITUITARY

MORPHOLOGY

- Morphology will vary widely depending on etiology

OTHER HIGH YIELD POINTS

- Hypophysitis secondary to drugs is most commonly caused by **immune checkpoint inhibitors**
  - Considered an immune-related adverse event
- Etiology can be infectious or systemic in nature
- Can result after a ruptured Rathke's cleft cyst

21. NON NEOPLASTIC SELLAR PATHOLOGY

MALFORMATIONS

EMPTY SELLA SYNDROME

MORPHOLOGY

- Primary empty sella syndrome is sometimes called **"arachnoidocele"**
  - ➢ Subarachnoid space herniates into sella turcica
  - ➢ Arachnoid membrane invaginates
  - ➢ Herniation compresses and **flattens pituitary gland**
  - ➢ **Pituitary stalk extension**
- Secondary empty sella syndrome occurs after necrosis or infarction of pre-existing pituitary adenoma
- Sella turcica appears **grossly empty**

OTHER HIGH YIELD POINTS

- Usually asymptomatic
- Can be caused by irradiation or resection of pituitary adenoma
- Imaging may demonstrate an enlarged sella turcica, **mimicking a pituitary adenoma**

PERSISTENCE OF RATHKE'S POUCH REMNANTS

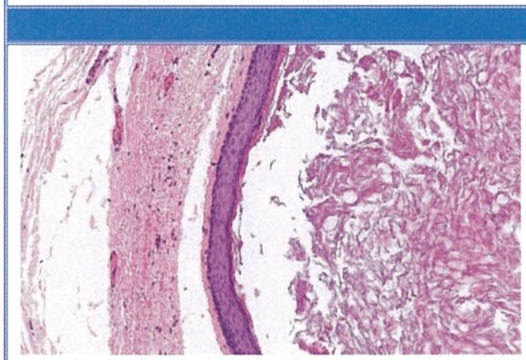
MORPHOLOGY

- Squamous cells arranged in small nests within the posterior pituitary lobe

OTHER HIGH YIELD POINTS

- Persistence of Rathke's pouch remnants is without clinical significance
- These remnants lack hormonal function
- Found in 30% of normal pituitaries on postmortem examination
- Rathke's pouch is an embryonic structure of ectodermal origin which gives rise to the:
  - ➢ Anterior pituitary gland
  - ➢ Intermediate gland
  - ➢ Pars tuberalis

CYSTS



H&E showing keratin debris and a squamous lining
Picture courtesy: Raquel T. Yokoda, MD

Path Presenter

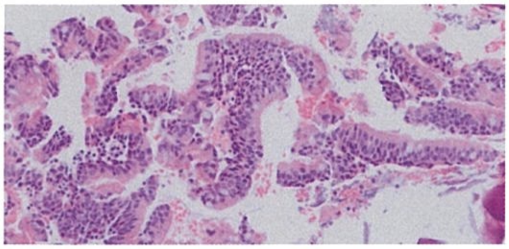
PITUITARY EPIDERMOID CYST

MORPHOLOGY

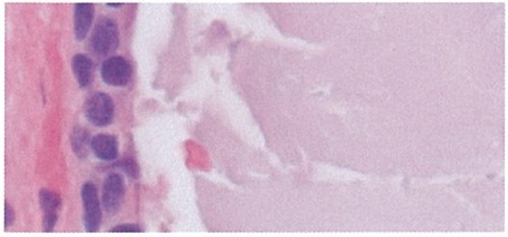
- Grossly thin-walled, round, unilocular, and pearly white
- Fibrous outer wall with a keratinizing squamous epithelial lining
- Lamellar keratin debris
- Without adnexae; called a **"dermoid cyst" if adnexae or hair present**
- **Cystic contents composed of anucleate squamous cells**

OTHER HIGH YIELD POINTS

- Epidermoid more common than dermoid cysts
- Mass effect can lead to hypopituitarism (pituitary compression) as well as visual changes and headache (suprasellar extension)
- Rare malignant degeneration
- Originates from ectopic or implanted epithelial cells
- **CK and EMA positive**



Rathke's cleft cyst wall
Picture courtesy: Benjamin B. Cho, MD



High-power view of cyst contents and epithelial lining

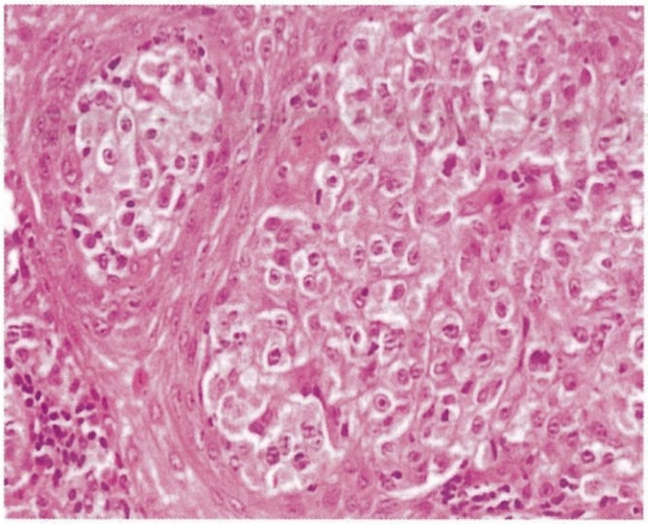
RATHKE'S CLEFT CYST

MORPHOLOGY

- Observed as an epithelial lining and often cystic structure separating the anterior and posterior pituitary
- Squamous tissue overlaid with focal, columnar, mucin-producing ciliated cells
  - ➢ Ciliated cells may be pseudostratified or simple
- Prone to **squamous metaplasia**
- Cystic contents are colloid or proteinaceous in nature
- Grossly well circumscribed with cystic contents that may be gelatinous or may resemble CSF

OTHER HIGH YIELD POINTS

- The Rathke's cleft "pinches off" from Rathke's pouch as it separates from the oral ectoderm during development
- This persistent cleft of Rathke's pouch fills with fluid and becomes a cyst
- Usually an incidental finding during postmortem examination
- **Nuclei are negative for beta catenin**
- **CK8, CK20, and EMA positive**
- Differential diagnosis: Colloid cyst, craniopharyngioma (papillary)

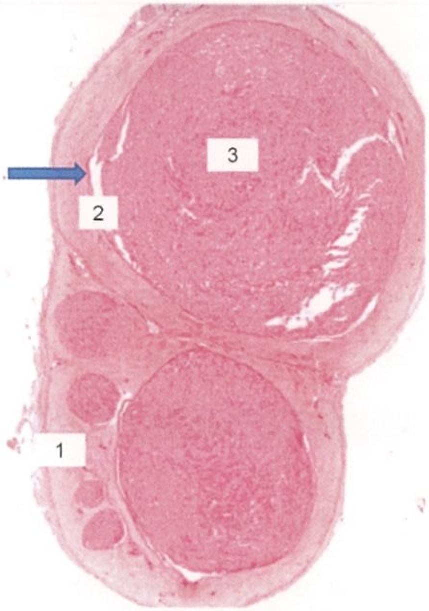


PERIPHERAL NERVE PATHOLOGY

VENKATESH DHANASEKARAN, MBBS
BALAN GASPAR, MBBS

22. PERIPHERAL NERVE PATHOLOGY

BASIC OVERVIEW

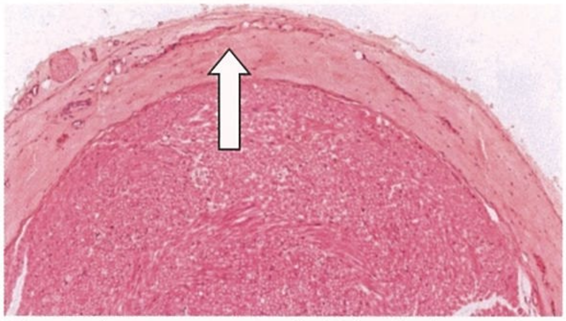


H&E stain depicting low-magnification image of a peripheral nerve with 1. Epineurium, 2. Arrow indicating perineurium, and 3. Endoneurial compartments

PERIPHERAL NERVE

MORPHOLOGY

- Peripheral nerves are composed of fascicles of nerve fibers
- Each nerve fiber contains axons surrounded by predominantly Schwann cells, which form myelin
- On histology, a nerve biopsy shows 3 distinct compartments which include epineurium, perineurium, and endoneurium
  - Epineurium: Predominantly a connective tissue that holds the nerve fascicles
  - Perineurium: Fibrous tissue that encircles the endoneurium
  - Endoneurium: Schwann cells, axons, capillaries, and occasional mast cells



H&E stain depicting perineurium (highlighted by the arrow)

IMMUNOHISTOCHEMISTRY & SPECIAL STAINS IN NERVE BIOPSY

Stain	Utility
Hematoxylin and Eosin	To identify the nature of the inflammation and its composition and granulomas
Masson Trichrome	To highlight fibrinoid necrosis in vasculitis and assess myelination
Luxol Fast Blue and Periodic Acid Schiff	To highlight the myelin (PAS is valuable to identify myelination in the small nerve fibers)
SOX10 and S100	Highlights Schwann cells
Martial Scarlet Blue	To identify fibrin of various ages
Elastic Van Gieson (EVG)	To highlight disruption of the internal elastic lamina within blood vessels in vasculitis
Congo Red	To highlight amyloid deposits
Oil Red O	To highlight degenerating myelin
EMA and GLUT1	Highlights perineurial cells
Neurofilament	Axons

22. PERIPHERAL NERVE PATHOLOGY

NERVE BIOPSY

NERVE BIOPSY

INDICATION

- Suspected hereditary neuropathies
- Vasculitis, amyloidosis, sarcoidosis, infection-related neuropathy
- Multifocal neuropathies in diabetes
- Neurolymphomatosis
- Monoclonal gammopathy

USUAL NERVES BIOPSIED

- Sural nerve
- Radial nerve

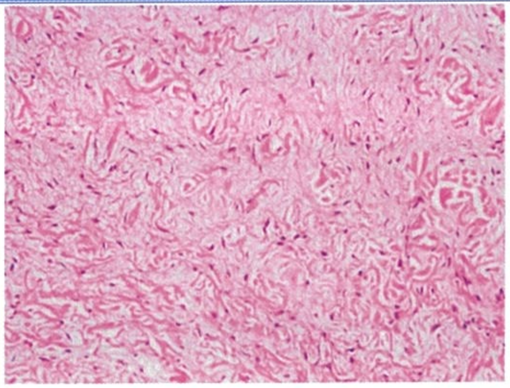
ANCILLARY STUDIES

- After biopsy, part of the tissue is fixed with formalin
- The remaining part of the nerve is fixed with glutaraldehyde for electron microscopy and fiber teasing
- Part of the nerve can also be snap-frozen for genetic studies

PREREQUISITES OF THE NERVE BIOPSY

- Complete clinical details, physical exam, and family history
- Nerve conduction studies, electromyography, and sensory studies
- CSF analysis
- Bone marrow studies, serum and plasma electrophoresis, immunofixation and serum free light chains for suspected monoclonal gammopathy
- ANCA and ANA serology for suspected vasculitis

PERIPHERAL NERVE PATHOLOGY



Traumatic neuropathy H&E showing Schwann cell proliferation
Picture courtesy: Balan Louis Gaspar, MD, DM

TRAUMATIC NEUROPATHY

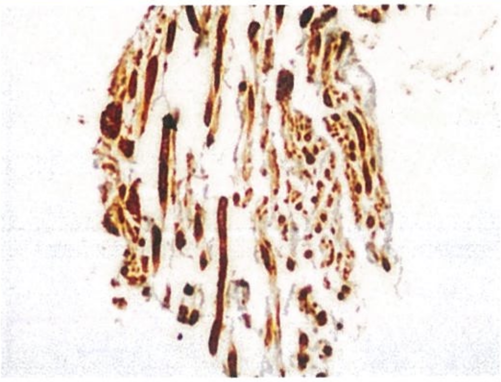
MORPHOLOGY

- Neuropraxic lesion shows demyelination of the axons admixed with intact axons → minor injury, excellent prognosis
- Axonotmesis lesion shows destruction of axons and myelin with intact endoneurium and perineurium → subjected to Wallerian degeneration distal and proximal to the injury → partial recovery expected
- Disruption of the entire axon, myelin, and components of the nerve with Schwann cell proliferation → sharp cut of the nerve, exposure to toxins → very poor recovery after surgical intervention
- There are no specific histopathologic findings

OTHER HIGH YIELD POINTS

- Occurs as a consequence of a traumatic injury to the nerve such as stretching, laceration, traction, contusion, or a combination
- Diagnosis of traumatic neuropathy is based on the constellation of clinical findings, temporal association with the trauma history, nerve conduction studies, and magnetic resonance imaging → **nerve biopsies are commonly not performed if there is substantial evidence for the diagnosis**

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)



Myelin basic protein immunostains in a CIDP patient
Picture courtesy: Balan Louis Gaspar, MD, DM

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

MORPHOLOGY

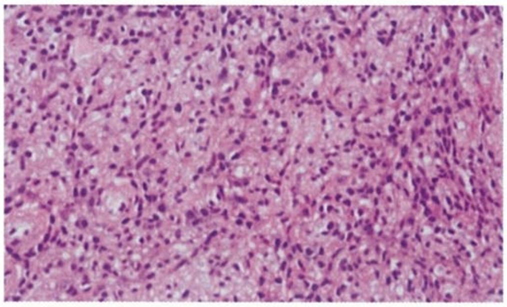
- Dominant demyelination in the form of thin myelin axons, naked neurons, and onion bulb formation (sign of chronic demyelination)
- Presence of macrophage-containing myelin degradation debris with endoneurial perivascular lymphocytic infiltrates
- Minimal to no axonal injury

OTHER HIGH YIELD POINTS

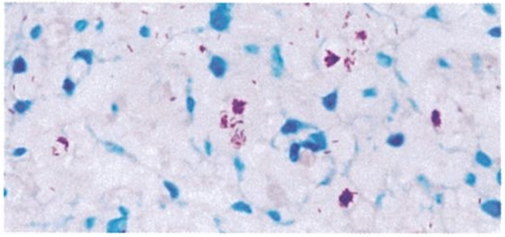
- CIDP is commonly diagnosed clinically
- Relapsing-remitting pattern of neuropathic disease that develops over years
- Clinically, there is sensory and motor involvement with areflexia
- Nerve biopsies are performed when clinicians must distinguish vasculitic neuropathy from Charcot-Marie-Tooth disease, a close mimic
- Predominant axonal involvement distinguishes from vasculitic neuropathy
- Non-uniform involvement of nerve bundles, macrophages engulfing myelin debris, endoneurial perivascular lymphocytic infiltrates, and abundant naked neurons distinguish from Charcot-Marie-Tooth disease

- When endoneurial perivascular lymphocytic infiltrates are sparse or minimal, CD45 immunohistochemistry helps to pick up the subtle lymphoid infiltrates

INFECTIOUS NEUROPATHIES



H&E shows inflammation and Virchow cells in lepromatous neuropathy



Fite-Faraco stain depicting numerous acid-fast M. leprae bacilli

Picture courtesy: Balan Louis Gaspar, MD, DM

LEPROMATOUS NEUROPATHY

MORPHOLOGY

- The spectrum varies from tuberculoid to lepromatous based on the patient's cell-mediated immune status
- In lepromatous leprosy, the affected nerves are loaded with bacilli with a collection of foam cells, mixed inflammatory cells, and fibrosis
- Fibrosis in lepromatous leprosy causes the affected nerve to enlarge
- Tuberculoid leprosy: There is a well-formed granulomatous response in the affected nerve and a lack of demonstrable organisms (efficient cell-mediated immunity)

OTHER HIGH YIELD POINTS

- Clinical: Loss of sensation in the area of the affected nerve
- Etiology: Mycobacterium leprae
- The bacilli have affinity for Schwann cells and endothelial cells of the endoneurium
- Most common form of neuropathy in economically poor countries
- Nerve biopsy is mandatory for the diagnosis of the pure neuritic form of leprosy, as these patients lack skin lesions
- Acute neuritis of the involved areas occurs as part of the lepra reactions, as there is improvement in the patient's cell-mediated immunity
- Polymerase chain reaction of heat shock protein 65 in nerve samples is most specific test to diagnose leprosy

HIV-ASSOCIATED NEUROPATHY

MORPHOLOGY

- Endoneurial and perineurial lymphocytic inflammation
- Axonal degeneration of variable degree in each nerve fascicle
- HSV cytopathic effect → herpes neuritis
- Secondary viral opportunistic infection, CMV inclusions → CMV neuritis

OTHER HIGH YIELD POINTS

- Clinical: Distal symmetric polyneuropathy
- Etiology: Multiple HIV-related factors, secondary infections such as CMV or HSV, drug-related
- Electron microscopy: Tubuloreticular inclusions in the endothelium (due to increased cytokine activity)

NUTRITIONAL DEFICIENCY NEUROPATHIES

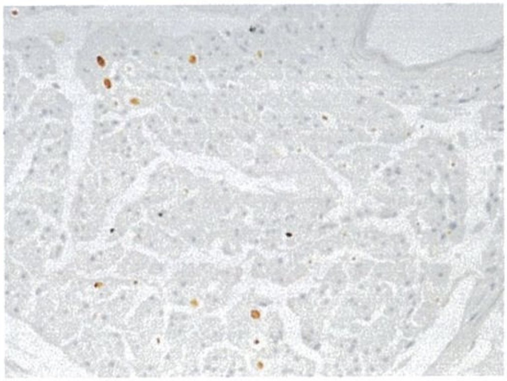
Vitamin	Clinical	Morphology
B12	• Subacute combined degeneration of the spinal cord, cognition abnormalities, and sensory neuropathies • Patients with pernicious anemia, vegetarian diet, or status post bariatric surgery	• Demyelination of the spinal cord • Vacuolization of neurons • Axonal degeneration
E	• Sensory-dominant polyneuropathy, nystagmus, and ataxia	• Degeneration of dominantly large myelinated fibers in peripheral nerves and spinal cord
Pyridoxine	• Deficiency: Absent reflexes, impaired sensation (patients treated with isoniazid for tuberculosis, patients in hemodialysis)	• Demyelination of the spinal cord • Vacuolization of neurons • Axonal degeneration
Niacin	• Diarrhea, dementia, dermatitis • Irritability, depression, cognitive abnormality	• Demyelination of the spinal cord • Vacuolization of neurons • Axonal degeneration

OTHER HIGH YIELD POINTS

- Consider nutritional deficiency in any patient status post small bowel surgery

22. PERIPHERAL NERVE PATHOLOGY

HEREDITARY NEUROPATHIES



Neurofilament immunostain showing severe degree of axonal loss
Picture courtesy: Balan Louis Gaspar, MD, DM

CHARCOT-MARIE-TOOTH DISEASE (CMT NEUROPATHY)

MORPHOLOGY

- No specific histopathologic features
- Recurrent episodes of demyelination and remyelination lead to the formation of myelin bulbs (numerous Schwann cell layers around axons) → increase in size of nerve fascicles
- Onion bulbs can be better appreciated via electron microscopy
- CMT-1 (demyelinating/hypertrophic form) is characterized by marked demyelination, remyelination, and onion bulb formation
- CMT-2 (neuronal form) characterized by loss of neurons in the anterior horn of the spinal cord and the ganglion; severe axonal loss in large myelinated fibers of affected nerves
- X-linked CMT does not show significant onion bulb formation, inflammation, or demyelination with axonal loss

OTHER HIGH YIELD POINTS

- Weakness and atrophy of distal leg muscles; many patients asymptomatic
- CMT-1 is related to PMP22 gene involved in the homeostasis of myelin
- CMT-1 can be differentiated from CIDP by diffuse involvement, lack of inflammatory infiltrates, and genetic testing
- CMT-2 → mutations in mitochondrial fusion protein 2
- CMT-2 → nerve conduction studies are classically > 38 milliseconds
- CMT-2 → late onset when compared with CMT-1
- X-linked CMT → connexin 32 mutation (helps in forming gap junctions) → decreased tendon reflexes, distal muscle weakness
- Medication can induce a CMT-like clinical picture (vincristine, metronidazole, nitrofurantoin) → essential to rule out before diagnosing CMT

FRIEDREICH ATAXIA

MORPHOLOGY

- Severe axonopathy of large myelin fibers with no features of demyelination

OTHER HIGH YIELD POINTS

- Autosomal recessive disease
- Mutation in the FXN gene (modulates oxidative stress)
- Progressive gait ataxia, difficult speech articulation, and diminished deep tendon reflexes

HEREDITARY NEUROPATHIES WITH PRESSURE PALSIES (HNPP)

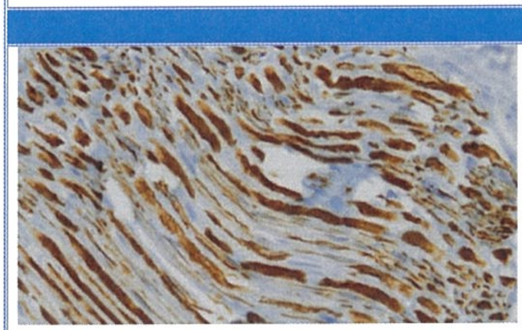
MORPHOLOGY

Axons with an increase in myelination at the circumference of the nerve fibers

OTHER HIGH YIELD POINTS

- Autosomal dominant disease
- Precipitated by injury to the nerve → usually resolves
- Slowly progressive, distally predominant sensorimotor neuropathy

OTHER NEUROPATHIES



Neurofilament immunostain showing marked axonal degeneration and loss. Picture courtesy: Balan Louis Gaspar, MD, DM

TOXIC NEUROPATHIES

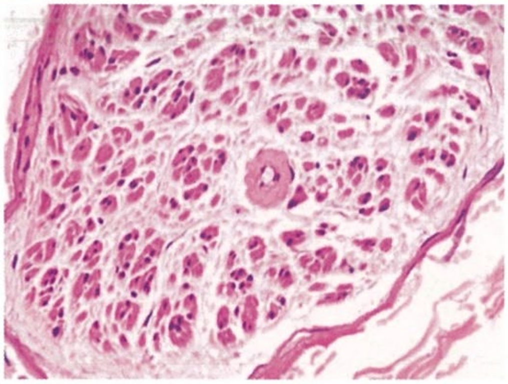
MORPHOLOGY

- No specific histopathologic features; usually shows axonal degeneration with regeneration, and presence of demyelination and inflammation is unusual

OTHER HIGH YIELD POINTS

- Clinical: Occurs following an exposure to endogenous agents (metals, medications, toxins); sensory symptoms predominate over motor symptoms
- Severity depends on the type of toxin
- Amiodarone toxicity is associated with lysosomal lipid inclusions in the Schwann cells, blood vessels, smooth muscle cells, and fibroblasts
- Chloroquine toxicity shows an accumulation of osmiophilic deposits in the epineurial blood vessels
- Presence of giant, swollen axons leads to consideration of hexacarbon, disulfiram, and acrylamide neuropathies

22. PERIPHERAL NERVE PATHOLOGY



H&E shows a hyalinized endoneurial blood vessel
Picture courtesy: Balan Louis Gaspar, MD, DM

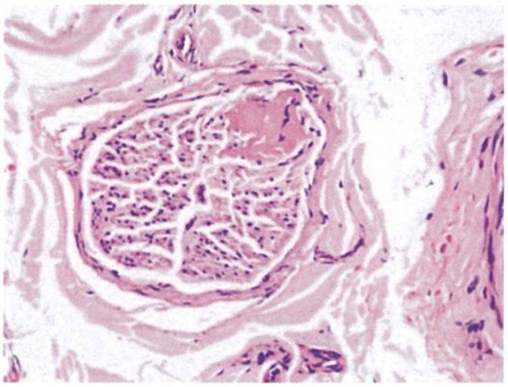
DIABETIC NEUROPATHY

MORPHOLOGY

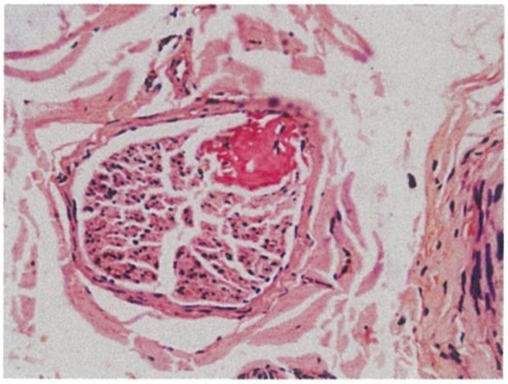
- Axonal degeneration with mild regeneration accompanied by depletion of large and small nerve fibers
- Thickening and hyalinization of the endoneurial small blood vessels
- Demyelination occurs in later stages

OTHER HIGH YIELD POINTS

- Clinical: Most common presentation 1) distal symmetric peripheral neuropathy; 2) diabetic polyradiculopathy (proximal neuropathy); 3) autonomic neuropathy; 4) mononeuropathy of any nerve, including cranial nerves
- Severity of neuropathy correlates with extent of endoneurial microvascular changes and poor glycemic control
- Electron microscopy: Thickening or reduplication of the endothelial basement membrane and axoglial dysfunction due to disruption of connections between myelin and axolemma of the nerve fibers



H&E shows eosinophilic amorphous deposits in the endoneurium



Congo red shows congophilia in the eosinophilic amorphous material

AMYLOID NEUROPATHY

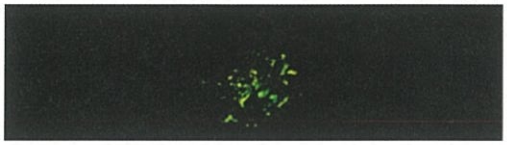
MORPHOLOGY

- Amyloid deposits in the subperineurial region and around the epineurial and endoneurial small blood vessels
- Can have features of axonal degeneration
- Lacks demyelination and inflammation
- Amyloid is confirmed by Congo red turning apple green under polarized light

AMYLOIDOSIS	CLINICAL
Primary	• Disease of old age (50-60 years) → polyneuropathy • Deposition of monoclonal immunoglobulin light chain secondary to plasma cell neoplasm
Secondary	• Associated with chronic systemic inflammatory diseases or chronic infectious diseases → isolated neuropathy • Deposition of serum amyloid A (SAA) protein
Familial	• Disease of middle age (30-40 years), positive family history • Deposition of mutant form of transthyretin, gelsolin, and apolipoprotein A1

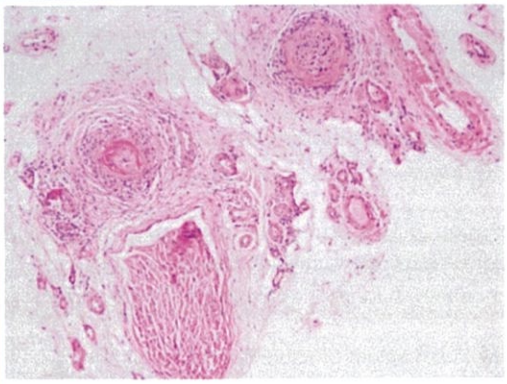
OTHER HIGH YIELD POINTS

- Mass spectrometry is necessary for the subtyping of the amyloid in the familial form
- Gelsolin-associated hereditary neuropathy has a characteristic medullary amyloid deposition in kidney and corneal lattice dystrophy

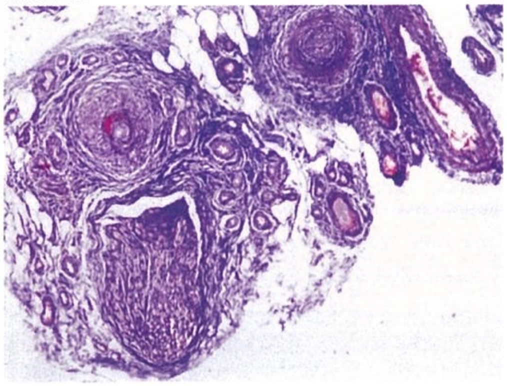


Apple green birefrigence of the amyloid depicted by polarizing microscope

22. PERIPHERAL NERVE PATHOLOGY



Fibrinoid necrosis of a vessel with inflammatory infiltrates



Masson trichrome highlights the fibrinoid necrosis in the vessel wall
Picture courtesy: Balan Louis Gaspar, MD, DM

VASCULITIC NEUROPATHY

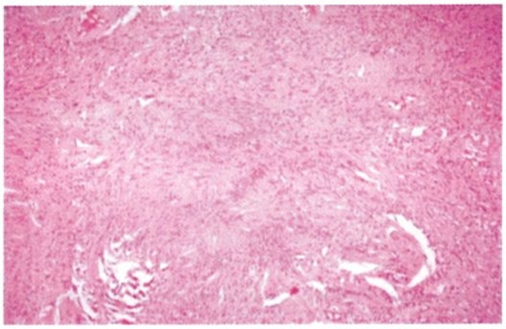
MORPHOLOGY

- Classic findings include fibrinoid necrosis, endothelial enlargement, transmural inflammatory infiltrates with fragmentation of neutrophils, and disruption of the internal elastic lamina
- Moderate to marked degree of axonal degeneration
- Inactive or late-stage lesions do not demonstrate classic findings
- Inactive or late-stage lesions may show medial fibrosis, intimal hyperplasia, hemosiderin deposition, and neovascularization of the epineurial connective tissue with fibrosis

OTHER HIGH YIELD POINTS

- Affects middle-aged to elderly individuals
- Asymmetric and multiple foci of nerve involvement
- Good response to immunosuppression
- Drugs and malignancy can precipitate vasculitis in the nerves
- Commonly affect the nerves: Churg Strauss syndrome, Wegener granulomatosis, polyarteritis nodosa, and microscopic polyangiitis
- Systemic vasculitis affecting small arteries and arterioles affects the nerves
- The vasculitic process in the nerve is subacute
- EVG and Perls' Prussian blue can help elucidate internal elastic lamina breaks in late-stage lesions

PERIPHERAL NERVE SHEATH TUMORS



H&E shows Antoni A hypercellular and Antoni B hypocellular areas

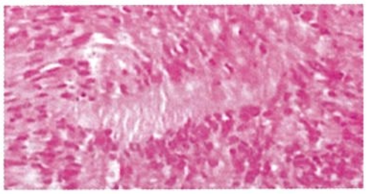
SCHWANNOMA

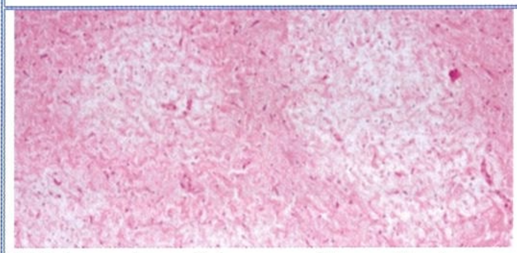
MORPHOLOGY

- Encapsulated spindle cell neoplasm; classically shows Antoni A (hypercellular) and Antony B (hypocellular loose myxoid) areas
- Verocay bodies, hyalinized blood vessels, perivascular hemosiderin

OTHER HIGH YIELD POINTS

- S100 and SOX10 positivity
- Multiple schwannomas (schwannomatosis) can arise in patients with SMARCB1 or LZTR-1 abnormalities
- Nuclear palisading demonstrated





H&E shows a hypocellular tumor with mucoid and collagenous background

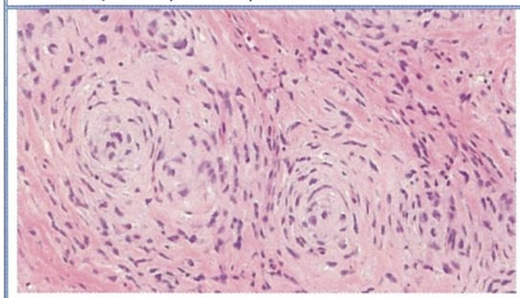
NEUROFIBROMA

MORPHOLOGY

- Interlacing bundles of elongated cells with wavy, dark-staining nuclei
- Stroma formed by wire-like strands of collagen with a small amount of mucoid material and shredded carrot-like collagen
- Without significant nuclear atypia, mitoses, or areas of necrosis
- Structures resembling Wagner-Meissner bodies or Pacinian corpuscles may be seen occasionally

OTHER HIGH YIELD POINTS

- Solitary, diffuse, and plexiform subtypes
- Plexiform neurofibroma is associated with neurofibromatosis type 1
- Patchy S100 positivity


H&E shows fascicles of bland spindle cells in perivascular whorls

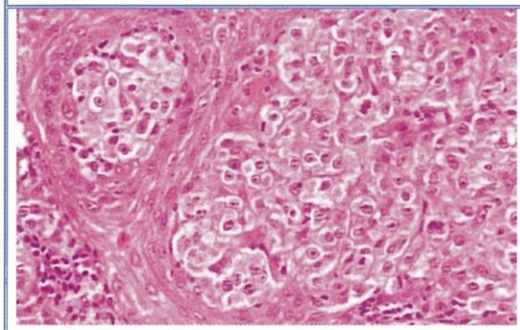
PERINEUROMA

MORPHOLOGY

- Benign tumor composed entirely of perineurial cells
- Storiform growth pattern; long fascicles with tumor cells arranged in lamellar fashion and perivascular whorls
- Lack of significant nuclear atypia, mitoses, or areas of necrosis

OTHER HIGH YIELD POINTS

- EMA and GLUT1 are positive
- GFAP and S100 are negative


H&E shows abundant granular cytoplasm

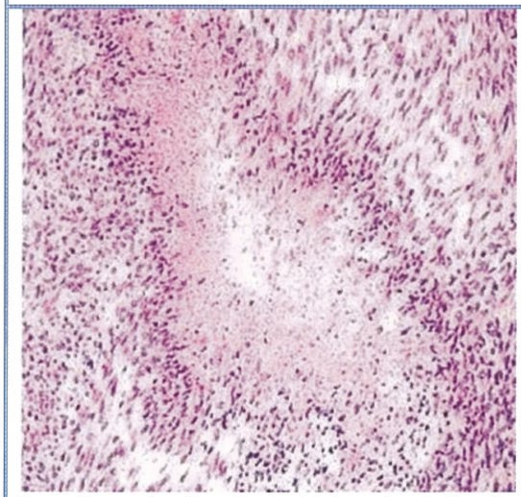
GRANULAR CELL TUMOR

MORPHOLOGY

- Composed of large oval or round cells with copious eosinophilic, distinctively granular cytoplasm
- Lack of nuclear atypia, mitoses, or necrosis

OTHER HIGH YIELD POINTS

- Benign tumor with neuroectodermal differentiation
- S100 and CD68 are positive


Areas of necrosis with palisading high-grade spindle cells

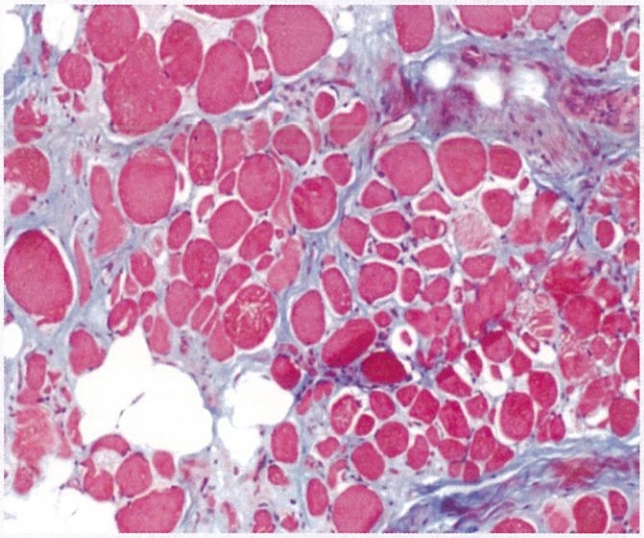
MALIGNANT PERIPHERAL SHEATH TUMOR

MORPHOLOGY

- Low power: Marbling pattern of spindle cells (low cellularity and hypercellularity) with large necrotic areas and viable tumor cells around vessels (peritheliomatous pattern)
- Wavy, buckled, comma-shaped, or asymmetrically oval nuclei with moderate to severe degree of atypia; light distinct cytoplasm
- Brisk mitotic activity

OTHER HIGH YIELD POINTS

- 5% of soft tissue sarcomas
- Low and high grade
- May arise in relation to nerve and in the background of the neurofibroma
- S100 and SOX10 are patchy positive
- Loss of H3K27me3 expression in tumor cells in the high-grade MPNST and retained in the low-grade MPNST



SKELETAL MUSCLE PATHOLOGY

ANKIT MALHOTRA, MBBS
JIE CHEN, MD

23. SKELETAL MUSCLE PATHOLOGY

TECHNICAL ASPECTS OF MUSCLE BIOPSY

TECHNIQUE OF BIOPSY

OPEN BIOPSY (PREFERRED)

- Approximately 1.5-2 cm x 0.5 cm of muscle belly
- Away from the myotendinous junction
- Wrap in **lightly soaked** saline gauze and transport immediately to the laboratory (within a few hours at 4-8°C)
- **Needle biopsy is not ideal**

SITE OF BIOPSY

- **Vastus lateralis** and **biceps brachii** are the most common muscles biopsied (superficial and easily accessible)
- Muscle with a moderate degree of pathology is preferred as it provides more information (severely affected muscle is predominantly fibrosed and fat infiltrated)
- Traumatized sites of EMG needles, recent injections, and previous surgery sites are avoided

PROCESSING OF BIOPSY

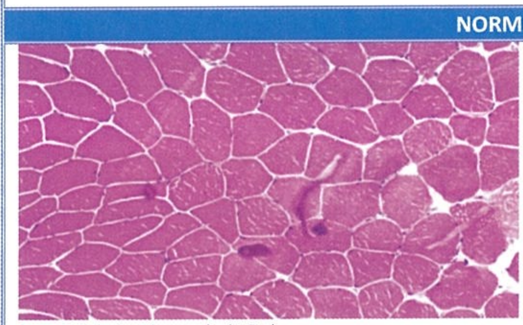
- Muscle biopsy is divided into 3 parts under a dissecting microscope:
    - ➢ **Frozen sections:** Cool isopentane in a small metal container to -160°C in liquid nitrogen and then snap freeze tissue for 20-30 seconds. Snap freezing avoids ice crystal formation and freeze artifacts. Once mounted on a cryostat, multiple sections are taken on different slides for the basic H&E stain and a battery of histochemical stains as listed in the table below. The remainder of the tissue is stored at -80°C for future tests, if necessary
    - ➢ **Formalin fixation**: Tissue is fixed in 10% buffered formalin fixative and embedded in paraffin blocks for regular histology and immunohistochemistry
    - ➢ **Electron microscopy**: Tissue is fixed in 2.5% buffered glutaraldehyde solution and preserved at 4°C

HISTOLOGICAL AND HISTOCHEMICAL STAINS USED IN MUSCLE BIOPSY

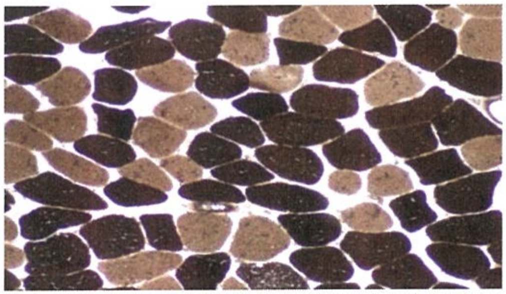
Stains Used on Fresh Frozen Muscle	Utility
Hematoxylin and Eosin (H&E)	Basic architectural and pathologic study
Modified Gomori Trichrome (MGT)	Ragged red fibers, nemaline rods, rimmed vacuoles, cytoplasmic bodies, reducing bodies, or tubular aggregates
Nicotinamide Adenine Dinucleotide Dehydrogenase (NADH)	Cores, target/targetoid fibers, moth-eaten fibers, ragged blue fibers, and tubular aggregates
Succinate Dehydrogenase (SDH)	Cores, ragged blue fibers, tubular aggregates
Cytochrome C Oxidase (COX) or Combined COX-SDH	Identification of COX-deficient fibers for mitochondrial abnormalities in mitochondrial myopathies
Periodic Acid Schiff (PAS) with/without Diastase	For glycogen storage myopathies
Congo Red	Amyloid deposition
Oil Red O	Lipid storage myopathies
Myophosphorylase	For glycogen storage disease type V (McArdle disease)
Acid Phosphatase	May indicate foci of degenerative/necrotic fibers within the muscle, macrophages, and lysosomes; useful in glycogen storage disorder type II (Pompe disease) and vacuolar myopathies

Alkaline Phosphatase	Usually positive in necrotic fibers, regenerating or non-innervated fibers, and perimysial tissue in inflammatory myopathies
Esterase	Neuromuscular and myotendinous junctions, small denervated cells
ATPase (pH 4.3, 4.6, and 9.4)	Fiber type grouping, fiber typing, type 1 or type 2 fiber atrophy
Phosphofructokinase	For glycogen storage disorder type VII (Tarui disease)
Menadione-Linked Alpha Glycerophosphate Dehydrogenase (MAG)	For reducing bodies

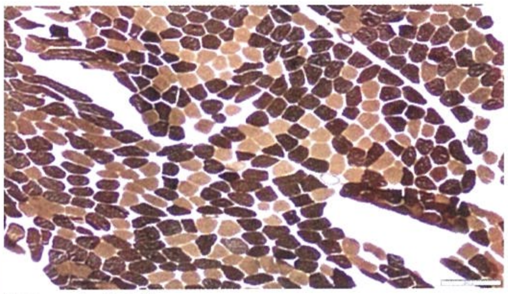
NORMAL ANATOMY AND HISTOLOGY OF MUSCLE



Normal skeletal muscle (H&E)



Normal checkerboard distribution of type 1 (light) and type 2 (dark) fibers (ATPase pH 9.4)



ATPase at pH 4.6

NORMAL ANATOMY AND HISTOLOGY

- **Epimysium**: The outermost connective tissue sheath
- **Perimysium**: Connective tissue containing multiple muscle fascicles along with arterioles, venules, nerves, and muscle spindles
- **Endomysium**: Scant connective tissue covering each muscle fiber
- Type 1 and type 2 fibers distributed in a **checkerboard** pattern
- Individual muscle fibers are round in children and polygonal in adults
- Nuclei usually peripherally located under the sarcolemma
- Approximately 3-4% of fibers show central nuclei
- Only minimal variation is found in normal muscle fibers
- Interstitial connective tissue is normally very scant

	Type 1 Fibers	Type 2 Fibers
Function	Slow-twitch	Fast-twitch
Color	Red	White
Glycogen Content	Low	High
Lipid Content	High	Low
Mitochondrial Content	High	Low
ATPase pH 9.4	Light	Dark
ATPase pH 4.6	Dark	IIa: Light IIb: Intermediate
ATPase pH 4.3	Dark	Light

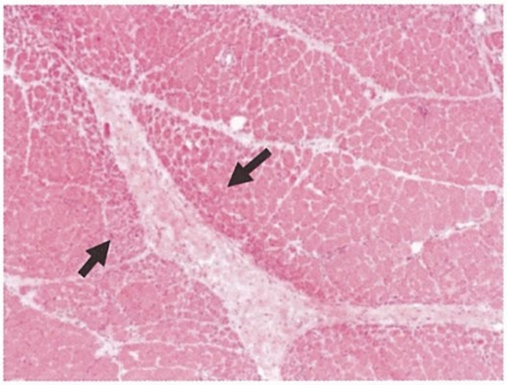
23. SKELETAL MUSCLE PATHOLOGY

MYOPATHIC VERSUS NEUROGENIC CHANGES

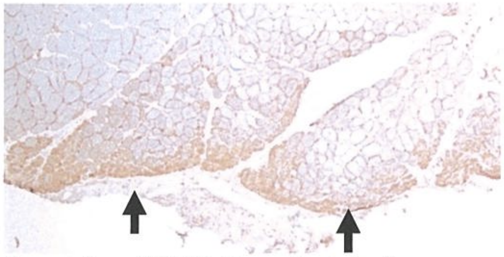
- Muscle pathologies can be broadly classified into primary myopathic or primary neurogenic
- Morphologic changes help distinguish between them
- Chronic or late stages of these diseases tend to show overlapping features with fibrosis and fat replacement

Myopathy	Neuropathy
Primary disorder of skeletal muscle	Primary disorder of nerves supplying the muscle
Rounded fibers	Angular atrophic fibers
Split fibers	Pyknotic nuclear clumps or nuclear bags
Increased internal nuclei	Atrophic or hypertrophic fibers in groups
Necrosis/myophagocytosis /regeneration	Target/targetoid fibers
Abnormal fibers are randomly distributed	Fiber type grouping
Inflammation	
Specific sarcoplasmic vacuoles and/or inclusions	

Picture courtesy: Timothy Richardson, DO, PhD



Perifascicular atrophy and inflammation
Picture courtesy: Timothy Richardson, DO, PhD



Upregulation of MHC-I in the perifascicular fibers

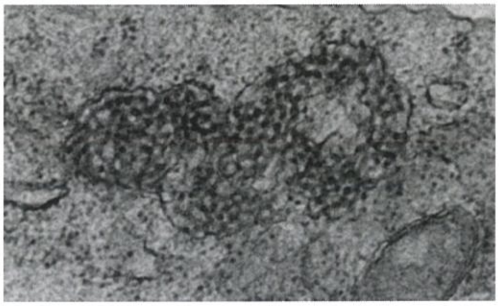
DERMATOMYOSITIS (DM)

MORPHOLOGY

- Histologic hallmark: **Perifascicular atrophy**
- Inflammation:
  - Perifascicular and perivascular
  - Predominantly CD4-positive T-lymphocytes and CD20-positive B-lymphocytes

OTHER HIGH YIELD POINTS

- Systemic disease is characterized by **skin** and **muscle** involvement
- The most common inflammatory myopathy in children
- It can be paraneoplastic in adults (check for visceral malignancies)
- Clinical presentation:
  - Subacute, symmetrical, proximal weakness
  - Characteristic skin rashes (**heliotrope periorbital edema, Gottron papules**, etc.)
  - Serology: MDA-5, SAE, TIF1-gamma, NXP-2, or Mi2 antibodies
- Histochemical stains:
  - Loss of COX reactivity and upregulation of MHC-I in the perifascicular fibers
  - Complement C5b-9 deposition in the perifascicular capillaries
- Electron microscopy:
  - Tubuloreticular inclusions in the endothelial cells



23. SKELETAL MUSCLE PATHOLOGY

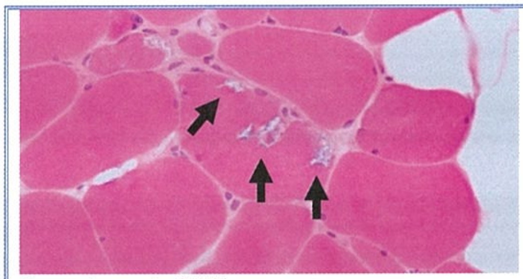
ANTISYNTHETASE SYNDROME

MORPHOLOGY

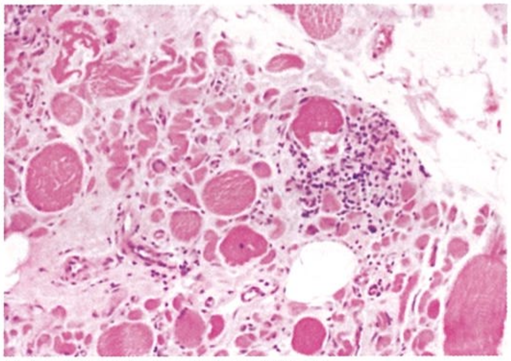
- **Perifascicular necrosis** with regenerating fibers
- Fragmentation of perimysial connective tissue
- Inflammation:
    - Perimysial extending into endomysial
    - Composed of T-lymphocytes, B-lymphocytes, and plasma cells

OTHER HIGH YIELD POINTS

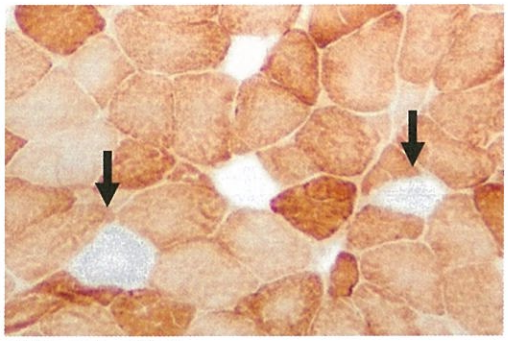
- Systemic manifestations common, including:
    - **Interstitial lung disease**
    - Mechanic's hands, Raynaud phenomenon
    - Arthralgias
- Less associated with malignancies than DM
- Serology: Autoantibodies against aminoacyl-tRNA synthetase (**Jo-1** most common, PL-7, PL-12, OJ, EJ, and others)
- Histochemical stains:
    - **Increased alkaline phosphatase** reactivity in the **perimysium**
    - MHC-I upregulation in the perimysium
    - C5b-9 deposition in the perimysial necrotic fibers
- Also known as "immune myopathies with perimysial pathology (IMPP)"



Rimmed vacuoles (H&E)



Endomysial inflammation and fibrosis



COX-negative fibers

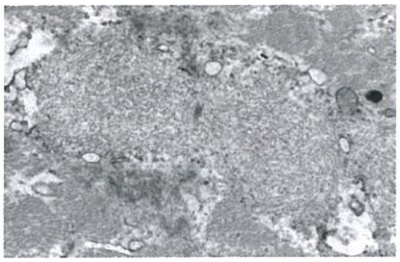
SPORADIC INCLUSION BODY MYOSITIS (sIBM)

MORPHOLOGY

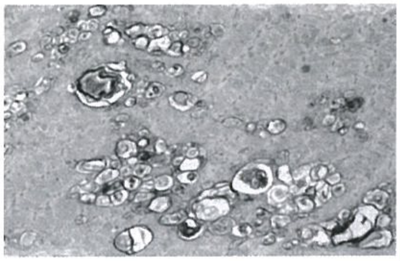
- Histologic hallmark: **Rimmed vacuoles** (best demonstrated on Gomori trichrome)
- **Chronic myopathic changes**:
    - Marked fiber size variation with hypertrophic fibers
    - Pyknotic nuclear clumps
    - Endomysial fibrosis and fatty infiltration
- Inflammation:
    - **Endomysial**
    - Predominantly CD8-positive T-lymphocytes

OTHER HIGH YIELD POINTS

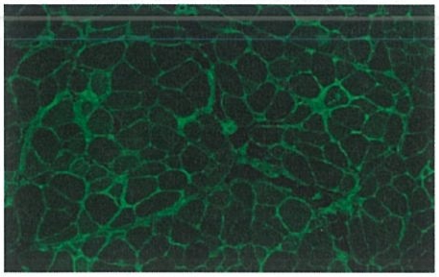
- **The most common inflammatory myopathy in patients over 50 years of age**
- Clinical presentation:
    - Slowly progressive, asymmetric atrophy of wrist flexors, finger flexors, and quadriceps
    - CK normal or mildly elevated
    - Often does not respond to immunosuppression
- Serology: Anti-cytosolic 5′-nucleotidase 1A (NC5C1A) in ~50% of patients
- Immunohistochemistry:
    - Cytoplasmic aggregates positive for **beta-amyloid, TDP-43, p62, LC3**
- Histochemical stains:
    - **Diffuse upregulation of MHC-I**
    - **Mitochondrial abnormality**: COX-negative fibers, ragged red fibers, ragged blue fibers
- Electron microscopy:
    - **Tubulofilamentous inclusions** (cytoplasmic or nuclear) with 15-20 nm filaments arranged in parallel or haphazardly (A)
    - Myelin-like whorls (B)



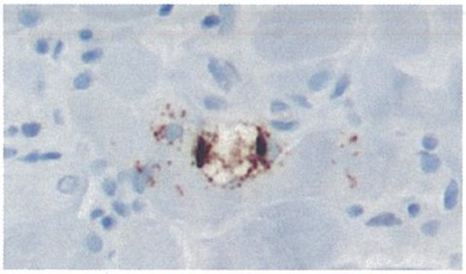
A)



B)



Diffuse upregulation of MHC-1



pTDP-43 positivity

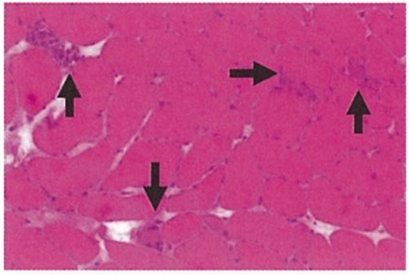
IMMUNE-MEDIATED NECROTIZING MYOPATHY (IMNM)/ NECROTIZING AUTOIMMUNE MYOPATHY (NAM)

MORPHOLOGY

- **Scattered necrotic fibers** at different stages of regeneration
- Inflammation:
  - **Absent or very mild** in comparison to the number of necrotic fibers
  - Can have frequent histiocytes

OTHER HIGH YIELD POINTS

- Clinical presentation:
  - Acute, severe weakness
  - High CK
  - Serology: **Anti-SRP** and **anti-HMG CoA reductase** autoantibodies
  - Anti-HMG CoA reductase may be associated with prior **statin** exposure; symptoms don't improve even after discontinuation of statin
- Histochemical stains:
  - Absent or patchy upregulation of MHC-I
  - Sarcolemmal C5b-9 deposition in scattered fibers



Scattered necrotic and regenerative fibers

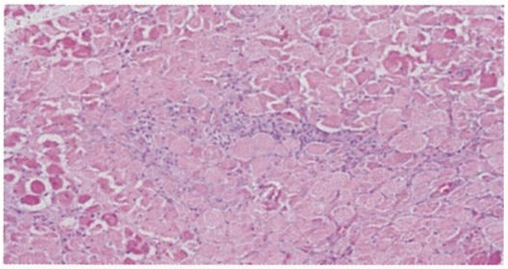
POLYMYOSITIS

MORPHOLOGY

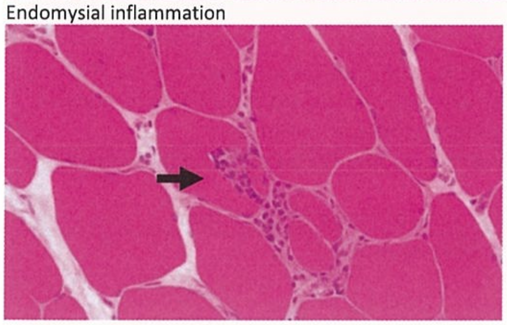
- Inflammatory myopathy that does not meet the criteria for DM or sIBM
- **Diagnosis of exclusion**
  - Endomysial inflammatory cells surrounding or invading non-necrotic fibers
  - Absence of perifascicular atrophy and rimmed vacuoles

OTHER HIGH YIELD POINTS

- Clinical presentation:
  - Subacute, symmetric, proximal weakness
  - High CK (10-50 times normal)



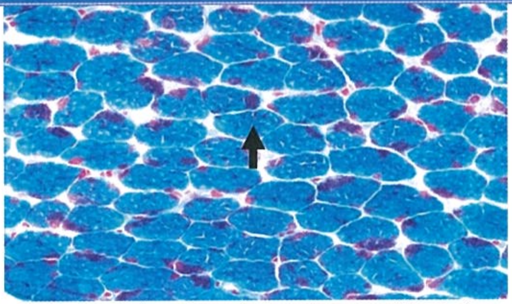
Endomysial inflammation

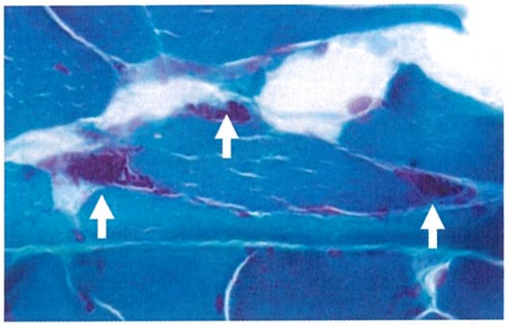


Inflammatory cells invading a non-necrotic fiber

23. SKELETAL MUSCLE PATHOLOGY

CONGENITAL MYOPATHIES


Nemaline rods (Gomori trichrome, low magnification)


Nemaline rods (Gomori trichrome, high magnification)

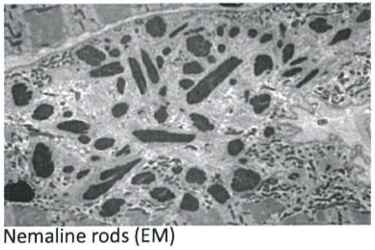
NEMALINE MYOPATHIES

MORPHOLOGY

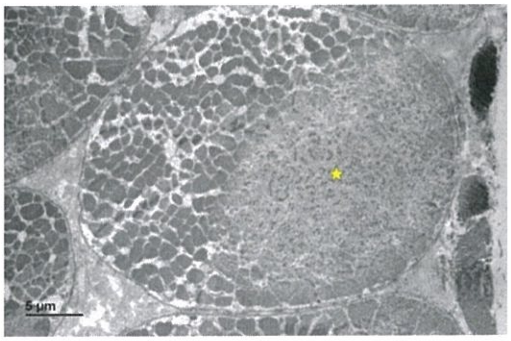
- Hallmark: Subsarcolemmal clusters of **nemaline rods**
  - Reddish-purple, thread-like inclusions in hypertrophic type 1 fibers
  - Best appreciated on modified Gomori trichrome stain (MGT)
- Type 1 fiber predominance

OTHER HIGH YIELD POINTS

- Classic presentation: Floppy infant with weakness and hypotonia
- **Sporadic, late-onset nemaline myopathy**
  - Can present in the 5th or 6th decade
  - It may be associated with monoclonal gammopathy or HIV infection
- Electron microscopy:
  - Rods are electron-dense, elongated inclusions with filaments attached at the periphery
  - Rods show square lattice structure on cross-section


Nemaline rods (EM)

Path Presenter



EM showing a myofiber with a single eccentric core area (star) with disorganization of myofilamentous pattern and paucity of mitochondria

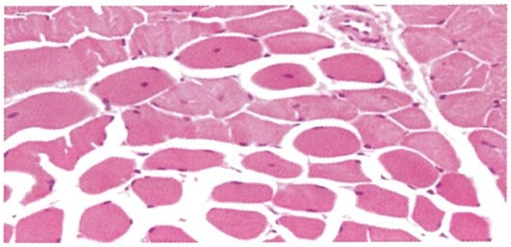
CORE MYOPATHIES

MORPHOLOGY

- Hallmark:
  - **Central core**: Single, centrally placed **core** (sarcoplasmic regions devoid of oxidative enzyme activity). Core extending along the length of myofiber in longitudinal sections
  - **Minicores**: More than one core per fiber. Can be subtle on H&E
- Type 1 predominance and selective type 1 atrophy/hypotrophy

OTHER HIGH YIELD POINTS

- Weakness and hypotonia often starting in infancy but may not manifest until early adulthood
- **Ryanodine receptor 1 (RYR1)** mutation in 50% of patients. Associated with **malignant hyperthermia**
- Histochemical stains:
  - Cores are negative for NADH, SDH, and COX but retain ATPase reactivity
- Electron microscopy: Cores are sarcoplasmic regions devoid of mitochondria
  - Structured cores: Preserved myofibrillar architecture
  - Unstructured cores: Distorted myofibrillar architecture with Z band streaming
  - Minicores: Multiple small areas of Z band irregularities



MYOTUBULAR/CENTRONUCLEAR MYOPATHIES

MORPHOLOGY

- Hallmark: Large, **centrally placed nuclei** in most fibers
  - Central nuclei regularly spaced down the fibers in longitudinal section
  - Central nuclei stain dark with oxidative enzyme and have pale, peripheral halos
- Type 1 predominance and selective type 1 atrophy/hypotrophy

OTHER HIGH YIELD POINTS

- X-linked myotubular myopathy:

  - Caused by mutations in MTM1 on the X chromosome, encoding myotubularin
  - Clinical presentation: Severe neonatal hypotonia
- Autosomal dominant centronuclear myopathy: Caused by mutations in DNM2 and some other genes. Various clinical presentation

Path Presenter

CONGENITAL FIBER TYPE DISPROPORTION

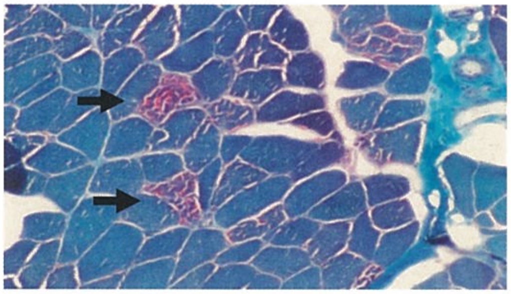
MORPHOLOGY

- Type 1 fiber predominance
- Selective type 1 atrophy with type 1 fibers at least 12% smaller in diameter than type 2 fibers

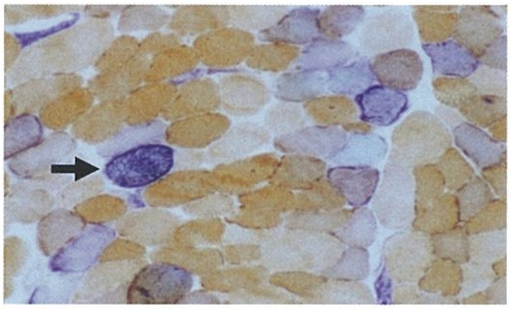
OTHER HIGH YIELD POINTS

- Associated with defects in SEPN1 (selenoprotein 1), RYR1 (ryanodine receptor 1), ACTA1 (alpha-actin 1), TPM2 (tropomyosin 2), TPM3 (tropomyosin 3), and some other genes
- Clinical presentation: Floppy infant syndrome, contractures
- Can be associated with other congenital myopathies

METABOLIC MYOPATHIES



Ragged red fibers on Gomori trichrome



COX-negative fibers and ragged blue fibers (combined COX and SDH stain)

Path Presenter

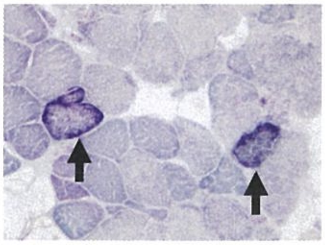
MITOCHONDRIAL MYOPATHIES

MORPHOLOGY

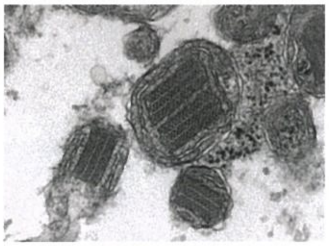
- **Ragged red fibers**
  - Reddish, subsarcolemmal aggregates of mitochondria
  - Best appreciated on Gomori trichrome
- **Ragged blue fibers** on NADH and SDH stains
- **COX-negative fibers**

OTHER HIGH YIELD POINTS

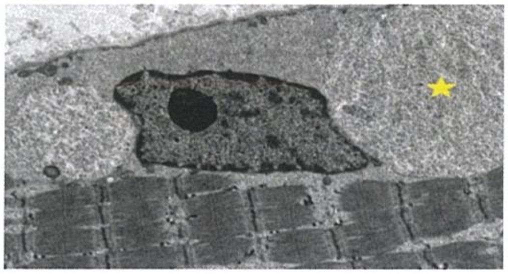
- Variable clinical presentations
- Common syndromes are:
  - Chronic progressive external ophthalmoplegia (CPEO)
  - Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
  - Myoclonic epilepsy and ragged red fibers (MERRF)
  - Kearns-Sayre syndrome (KSS)
- A few fibers with mitochondrial abnormality can also be part of normal aging
- Electron microscopy:
  - Subsarcolemmal aggregation of mitochondria
  - **Paracrystalline inclusions** forming "parking lot" structures
  - Abnormal concentric arrangement of cristae



Ragged blue fibers (SDH)



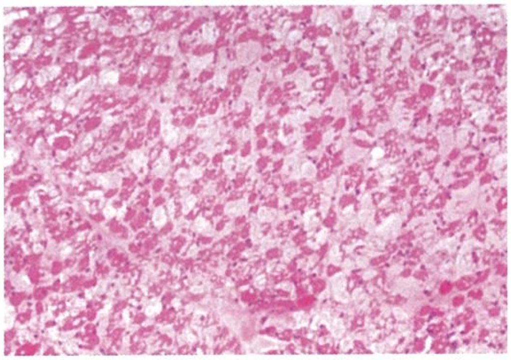
Paracrystalline inclusions



GLYCOGEN STORAGE MYOPATHIES

MORPHOLOGY

- **Subsarcolemmal vacuoles (blebs) containing faint granular material**
- Better appreciated on Gomori trichrome than H&E
- Glycogen particles can be confirmed by PAS stain and electron microscopy
- **McArdle disease** (**myophosphorylase** deficiency; glycogen storage disease type V)
  - Increased subsarcolemmal and intersarcomeric free glycogen
  - Complete loss of myophosphorylase activity in the muscle fibers



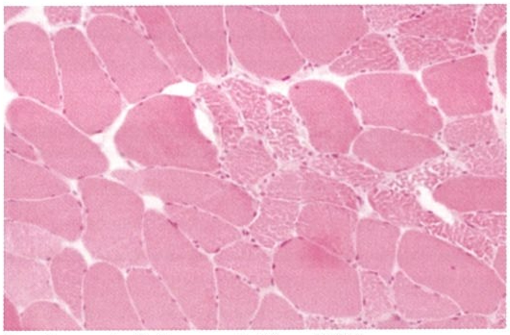
Glycogen particles highlighted by PAS

- **Late-onset Pompe disease** (**acid maltase** deficiency; glycogen storage disease type II)
  - A type of autophagic vacuolar myopathy
  - Prominent lysosomes highlighted by acid phosphatase stain
  - Membrane-bound glycogen within lysosomes on electron microscopy

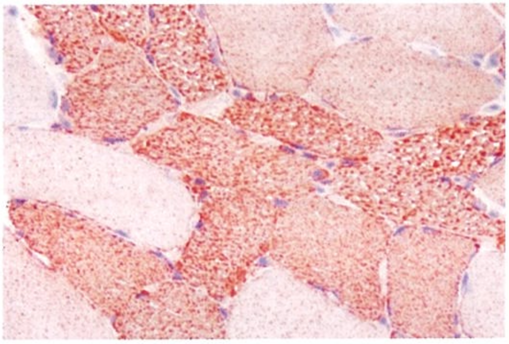
OTHER HIGH YIELD POINTS

- McArdle disease presents with episodes of exercise intolerance, muscle cramping, and rhabdomyolysis
  - Disorder of glycogen utilization
- Pompe disease presents with progressive proximal muscle weakness and atrophy
  - Accumulation of glycogen in lysosomes

Path Presenter



Small vacuoles in the muscle fibers (H&E)



Small lipid droplets highlighted by oil red O

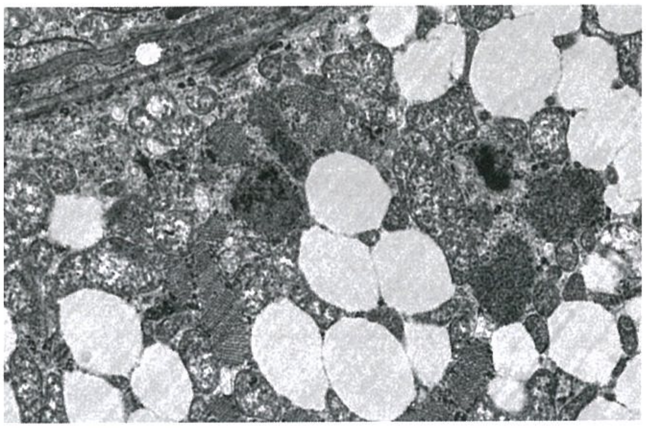
LIPID STORAGE MYOPATHIES

MORPHOLOGY

- Small lipid droplets evenly distributed within the muscle fibers
- More obvious in type 1 fibers

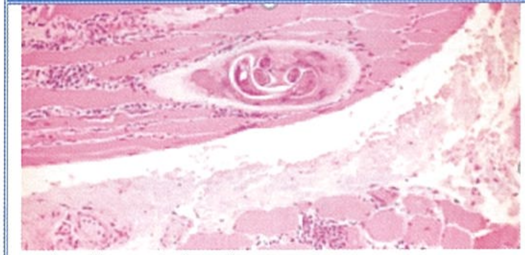
OTHER HIGH YIELD POINTS

- Can be associated with acquired (most common) or hereditary conditions
  - Acquired: Malnutrition, chronic kidney disease, cirrhosis, etc.
  - Hereditary: Primary carnitine deficiency, multiple acyl-CoA dehydrogenase deficiency, etc.
- Lipid droplets can be visualized by oil red O or Sudan black stains



Path Presenter

INFECTIOUS MYOPATHY



Trichinella spiralis (H&E)

TRICHINELLOSIS/TRICHINOSIS

MORPHOLOGY

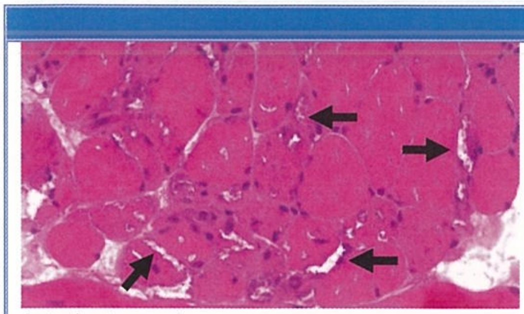
- Encysted larvae ("nurse" cells) within muscle fibers
- Neighboring muscle fibers show mononuclear inflammation

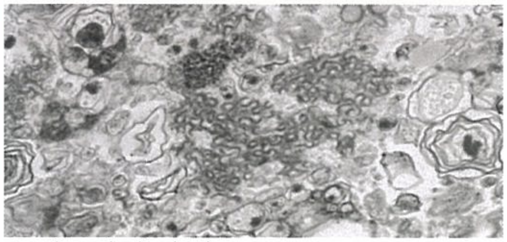
OTHER HIGH YIELD POINTS

- Most frequent parasitic myositis
- Caused by ingestion of meat infested with a roundworm Trichinella spiralis
- Larval forms enter the bloodstream by penetrating the gut wall and making their home in skeletal muscle fibers
- Lie dormant (not active, latent)
- Cause generalized muscle and body aches

23. SKELETAL MUSCLE PATHOLOGY

TOXIC MYOPATHIES


Autophagic vacuoles


Curvilinear bodies (EM)

CHLOROQUINE/HYDROXYCHLOROQUINE (CQ/HCQ) TOXIC MYOPATHY

MORPHOLOGY

- A type of **autophagic vacuolar myopathy**
- Increased lysosomal activity highlighted by **acid phosphatase**
- Necrosis may occur
- Vacuoles contain membranous, myelin-like whorls and cell debris
- **Curvilinear bodies** on electron microscopy

OTHER HIGH YIELD POINTS

- CQ and HCQ are commonly used to treat autoimmune diseases and malaria; they are degraded in lysosomes
- Clinical presentation: Myopathy, restrictive cardiomyopathy, peripheral neuropathy
- Curvilinear bodies are also seen in **neuronal ceroid lipofuscinosis**, an inherited disorder characterized by accumulation of autofluorescent ceroid lipofuscin-like material in neurons and other cell types

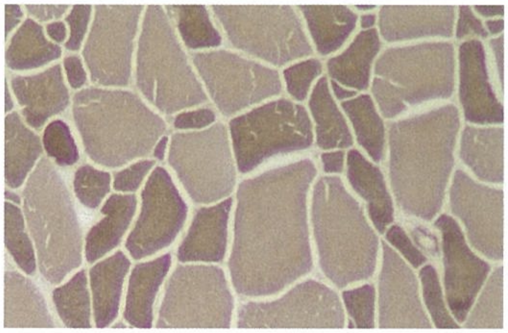
STATIN-INDUCED MYOPATHY

MORPHOLOGY

- Myofiber necrosis, myophagocytosis
- Occasional regenerating fibers
- Inflammation (predominantly CD8-positive T-lymphocytes) around the myofibers

OTHER HIGH YIELD POINTS

- Caused by **direct toxic** insult to myofibers by statins
- Clinical presentation:
    - Rhabdomyolysis, elevated CK, myalgias
    - **Reversible** after withdrawal of statins
    - Rare cases develop statin-induced autoantibodies against **HMG CoA reductase enzyme** (immune-mediated necrotizing myopathy)
- MHC-I may be upregulated, signifying heightened inflammatory activity


Type 2 (dark) fiber atrophy (ATPase pH 9.4)

STEROID-ASSOCIATED MYOPATHY

MORPHOLOGY

- Selective **type 2 fiber atrophy**
- Selective **loss of myosin thick filaments** from the A bands on electron microscopy

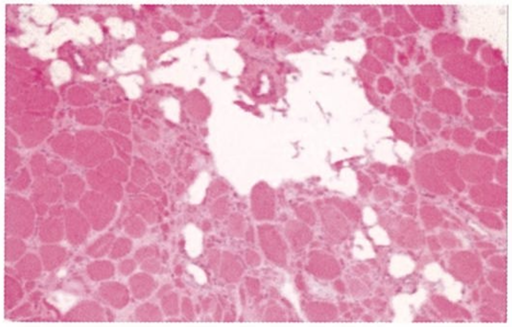
OTHER HIGH YIELD POINTS

- Seen in critically ill and ICU patients treated with corticosteroids (critical illness myopathy)

Type 2 fiber atrophy is also observed in muscle disuse, aging, acute denervation, some collagen vascular diseases, myasthenia gravis, alcohol toxicity, and systemic malignancy

MUSCULAR DYSTROPHIES

Severe fiber size variation and fat infiltration



DUCHENNE MUSCULAR DYSTROPHY (DMD)

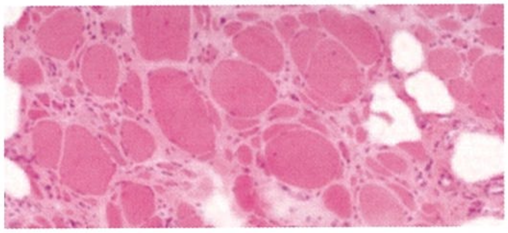
MORPHOLOGY

- Chronic myopathic changes
    - Severe variation in fiber sizes: Atrophic fibers mixed with rounded, hypertrophic fibers
    - Increased internal nuclei
    - Small foci of necrotic fibers and regenerating fibers
    - Increased endomysial connective tissue with fatty infiltration

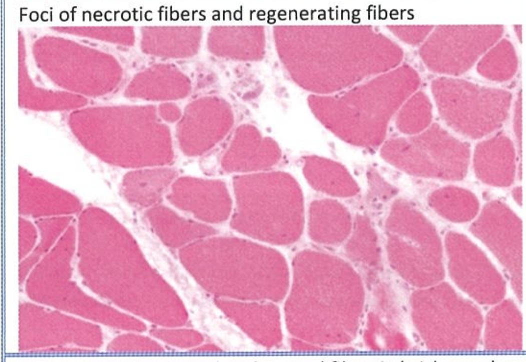
OTHER HIGH YIELD POINTS

- Dystrophin is part of the **dystrophin-glycoprotein complex** that connects the basement membrane to the cytoskeleton
- The dystrophin gene (DMD) is the longest gene identified in the human genome
- DMD is the most common **X-linked** dystrophinopathy

Increased endomysial connective tissue

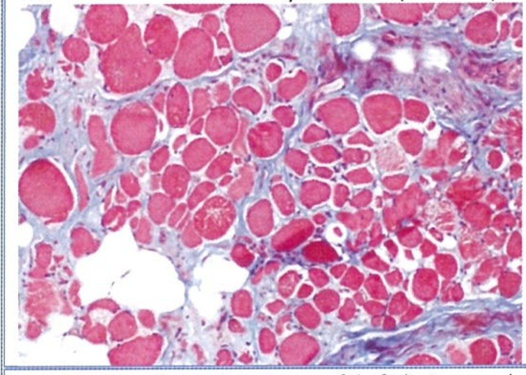


Foci of necrotic fibers and regenerating fibers



- Caused by mutations in dystrophin leading to an early stop codon or frameshift, resulting in **complete loss of dystrophin protein**
- Clinical presentation:
  - Early onset of severe muscle weakness with pseudohypertrophy in the calves
  - May result in cardiac dysfunction
  - Markedly elevated CK (often > 10,000)
  - Can lead to death in young adulthood
- Western blotting and genetic testing are used to detect different mutations
- Immunohistochemistry:
  - Complete loss of subsarcolemmal staining of all antibodies against different domains of dystrophin (including antibodies against the C-terminus, N-terminus, or the rod domain)
  - A few revertant fibers that retain expression of dystrophin may be present
  - Retained expression of spectrin suggestive of membrane integrity
  - Female carriers show a mosaic pattern of mixed dystrophin-positive and dystrophin-negative fibers

Fiber size variation and endomysial fibrosis (trichrome)



BECKER MUSCULAR DYSTROPHY (BMD)

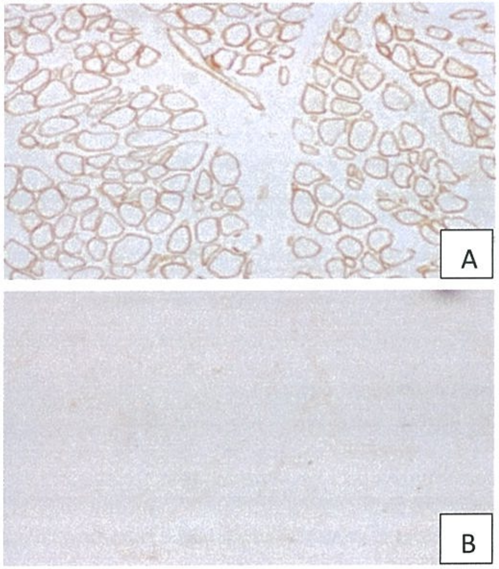
MORPHOLOGY

- Variable morphology

OTHER HIGH YIELD POINTS

- Milder form of the X-linked dystrophinopathies
- Caused by mutations in the DMD gene resulting in expression of less dystrophin or shortened, only **partially functional dystrophin**
- Clinical presentation: Later onset, longer course, and less severe than DMD
- Immunohistochemistry:
  - **Reduced or variable expression of dystrophin** between different fibers and within the same fiber
  - Multiple antibodies are required for characterization

A) Normal sarcolemmal expression of dysferlin in control muscle; (B) Absent dysferlin in a dysferlinopathy patient



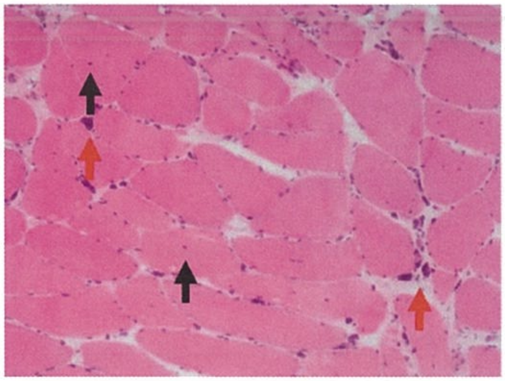
LIMB GIRDLE MUSCULAR DYSTROPHY (LGMD)

MORPHOLOGY

- Chronic active myopathy with necrosis/regeneration and endomysial fibrosis
- **Dysferlinopathy** (LGMD2B):
  - May show inflammatory infiltrate and MHC-I upregulation, leading to misdiagnosis of an inflammatory myopathy
  - May show amyloid deposition
  - Complete loss of sarcolemmal expression of dysferlin

OTHER HIGH YIELD POINTS

- A diverse group of more than 30 different diseases
- Can be autosomal recessive or autosomal dominant
- Onset frequently in the 2nd or 3rd decade with **proximal pelvic girdle muscle weakness,** markedly elevated CK (can be up to several hundred times normal)
- Dysferlinopathies, sarcoglycanopathies, and dystroglycanopathies most common



Multiple internal nuclei (black arrows) and marked pyknotic nuclear clumps (red arrows)
Picture courtesy: Raquel Yokoda, MD

MYOTONIC DYSTROPHY (DM)

MORPHOLOGY

- Significantly **increased internal nuclei**
- DM1:
  - Atrophy is more obvious in type 1 fibers
  - Frequent ring fibers
  - Sarcoplasmic masses: Dark-stained zones consisting of disorganized myofibrils, ribosomes, and dilated sarcoplasmic reticulum
- DM2:
  - Atrophy is more obvious in type 2 fibers
  - Early onset of markedly atrophic fibers and pyknotic nuclear clumps

OTHER HIGH YIELD POINTS

- Autosomal dominant
- Clinical presentation:
  - Myotonia (sustained involuntary contraction of a group of muscles)
  - Muscle weakness and wasting
  - Childhood cataracts, endocrinopathy, and cardiomyopathy
- DM1:
  - Most common form of adult-onset muscular dystrophy
  - Incidence: 1 in 10,000
  - Caused by trinucleotide repeat expansion of CTG at the 3' end of myotonic dystrophy protein kinase (DMPK) gene on chromosome 19q
  - Has a congenital form
  - Anticipation: Successive generations have more repeats and show more severe symptoms
- DM2:
  - Caused by repeat expansion of CCTG of the ZNF9 gene on chromosome 3q
  - Size of repeats correlates with age of onset and disease severity

OTHER RARE DYSTROPHIES

EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD)

- Caused by mutations in LMNA (laminin), EMD (emerin), and other genes
- Affects muscles of the shoulder and lower leg, causing humero-peroneal weakness along with contractures of the elbow and Achilles tendon

FACIOSCAPULOHUMERAL DYSTROPHY (FSHD)

- Caused by defective FSHD1 or FSHD2 gene
- Affects the facial muscles and muscles of shoulder girdle

ULLRICH CONGENITAL MUSCULAR DYSTROPHY (UCMD)

- Caused by mutations in the genes encoding collagen VI (COL6A1, COL6A2, and COL6A3), an extracellular matrix protein
- Immunohistochemistry:
  - Reduced collagen VI reactivity in the endomysium or sarcolemma, better appreciated with double labelling of another extracellular matrix protein such as perlecan

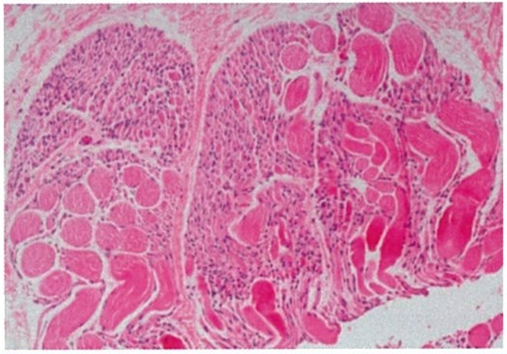
ALPHA-DYSTROGLYCAN DEFICIENT CONGENITAL MUSCULAR DYSTROPHY

- Caused by defective O-linked glycosylation of alpha-dystroglycan protein, a component of the sarcolemmal dystrophin-associated complex
- Defect is in the myofiber receptor for the extracellular matrix component
- Associated with brain and eye anomalies

23. SKELETAL MUSCLE PATHOLOGY

NEUROGENIC DISORDERS

Picture courtesy: Timothy Richardson, DO, PhD



SPINAL MUSCULAR ATROPHY (SMA)

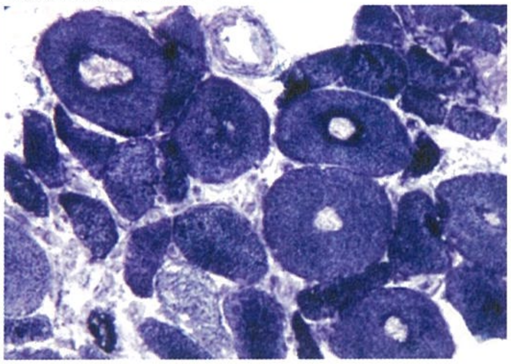
MORPHOLOGY

- Large groups or fascicles of round, severely atrophic fibers
- Scattered hypertrophic fibers

OTHER HIGH YIELD POINTS

- Autosomal recessive (incidence: 1 in 6,000)
    - Most cases caused by deletion of exon 7 in **survival motor neuron (SMN1)** gene, causing cell death in alpha motor neurons of the spinal cord and subsequent denervation of the muscle
- 3 major clinical groups depending on severity:
    - Type I (Severe): Severe hypotonia in early infancy
    - Type II (Intermediate): Hypotonia at 6-12 months
    - Type III (Mild): Later onset

Target/targetoid fibers on NADH stain



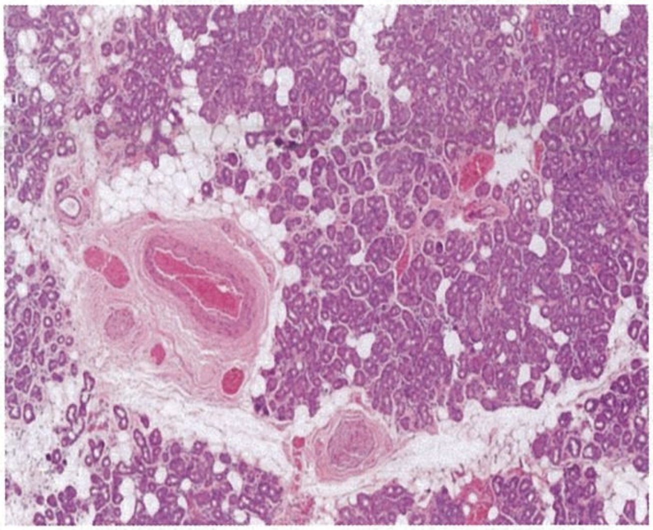
DENERVATION ATROPHY

MORPHOLOGY

- Denervation:
    - **Angular atrophic fibers** that are **scattered** or in **small groups**
- Reinnervation:
    - **Fiber type grouping**: Separate groups of type 1 or type 2 fibers; best seen on ATPase stains
    - **Target fibers**: 3 concentric zones on NADH stain
- Chronic myopathic changes such as myonecrosis, endomysial fibrosis, and fat infiltration may occur in long-standing neurogenic atrophy

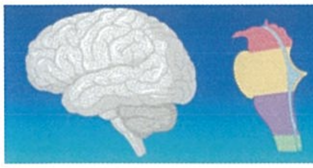
OTHER HIGH YIELD POINTS

- Muscle changes and nerve changes may be temporally dissociated throughout the disease's chronic course



EYE PATHOLOGY

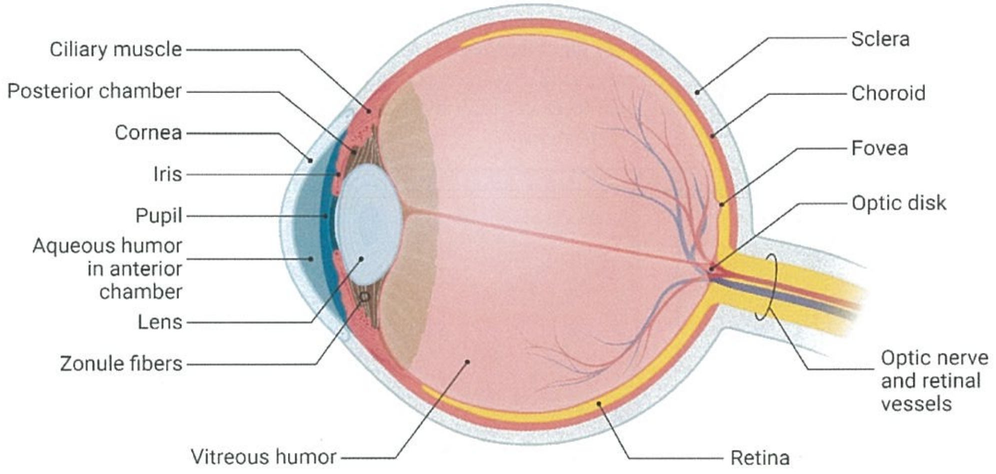
RAQUEL T. YOKODA, MD
CODRIN E. IACOB MD



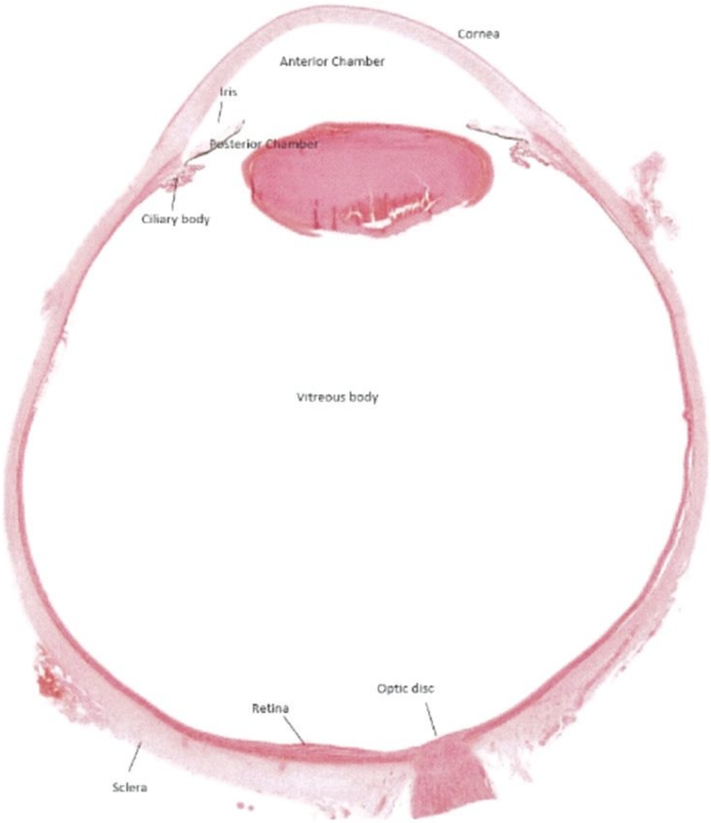
24. EYE PATHOLOGY

EYE PATHOLOGY: NORMAL ANATOMY & HISTOLOGY

Anatomy of the Human Eye


Ciliary muscle
Posterior chamber
Cornea
Iris
Pupil
Aqueous humor in anterior chamber
Lens
Zonule fibers
Vitreous humor
Sclera
Choroid
Fovea
Optic disk
Optic nerve and retinal vessels
Retina

Created with BioRender


Cornea
Anterior Chamber
Iris
Posterior Chamber
Ciliary body
Vitreous body
Optic disc
Retina
Sclera

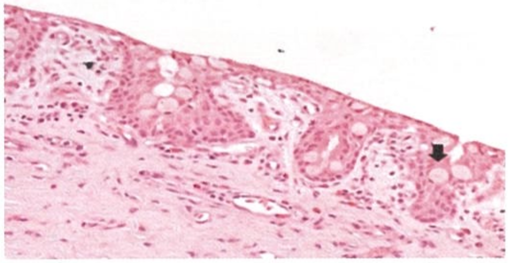
H&E shows normal eye histology

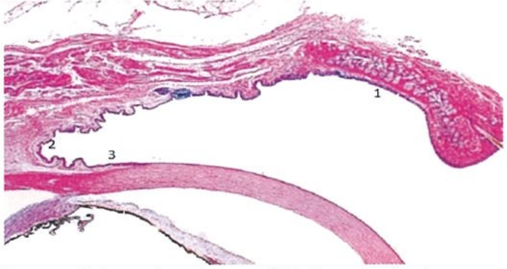
GENERAL OVERVIEW

- At birth, the anterior-posterior diameter of the eye is 17 mm; at 2 years old it is 22 mm; adult eye is 24 mm
- There are 3 layers surrounding the vitreous humor, lens, and the spaces that form the anterior and posterior chamber
  - ➢ **Outermost layer:** Composed of the transparent cornea and the white sclera
  - ➢ Middle layer: Uvea (uveal tract) is composed of the iris, ciliary body, and choroid
  - ➢ **Innermost layer:** The retina is in direct contact with the vitreous humor
- The central retina contains the macula (macula lutea) which harbors in its center the fovea (fovea centralis)
- The **fovea/macula lutea** contains a very high concentration of cones. These light-sensitive cells in the retina give detailed central vision
- The macula is the yellow oval spot (clinical exam) at the center of the retina
- The optic disc (blind spot) is the insertion of the optic nerve

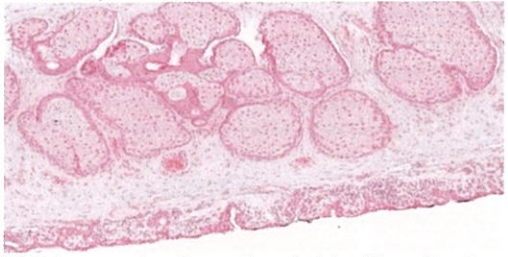
Path Presenter

24. EYE PATHOLOGY


Conjunctival mucous membrane on H&E showing non-keratinizing stratified epithelium with goblet cells (goblet cell highlighted with arrow)



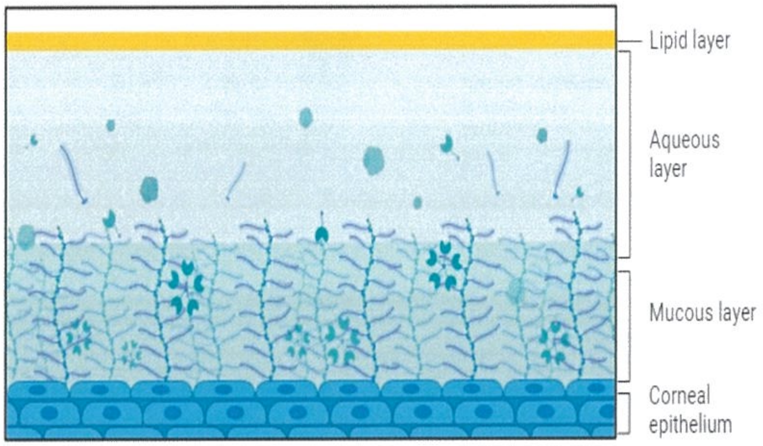
3 parts of the conjunctiva on H&E: The palpebral conjunctiva (1), the forniceal conjunctiva (2), and the bulbar conjunctiva (3)


H&E shows conjunctiva and tarsal plate with meibomian glands

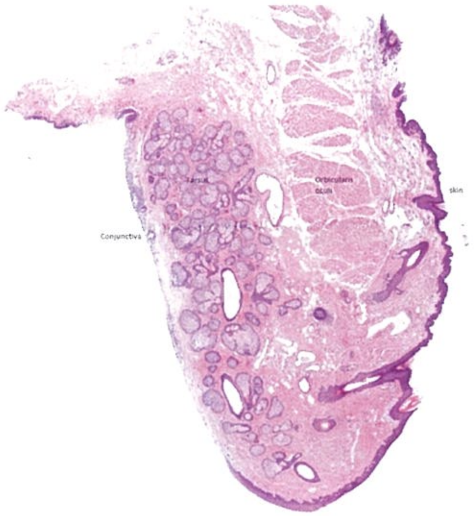
CONJUNCTIVA

- Conjunctiva: A mucous membrane with goblet cells
- Surface: Non-keratinizing stratified epithelium with goblet cells, Langerhans cells (dendritic-appearing), and few dendritic melanocytes
- Stem cells are located in the limbus and generate corneal epithelium. Limbal stem cell deficiency leads to conjunctivalization of corneal epithelium
- Homeostasis of the conjunctiva is dependent on a healthy tear film
- Tear film has 3 layers: Mucoid (closely associated with the corneal epithelium, ensures lubrication for blinking), aqueous (middle, ensures antisepsis), and lipid layer (air interface, avoids premature evaporation)

Tear film layers



- In diabetic patients, the tear film is abnormal, which contributes to dry eye; diabetes is a major risk factor for dry eye



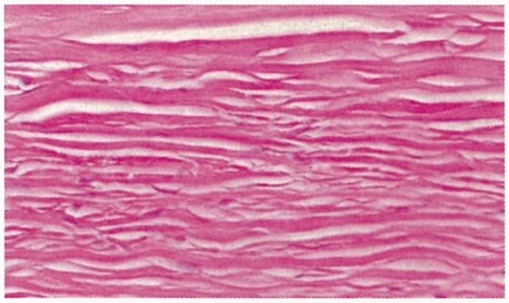
H&E shows skin, orbicularis oculi muscle, the tarsus, and palpebral conjunctiva

EYELID & LACRIMAL GLAND DRAINAGE

- The eyelid can be divided into conjunctival and cutaneous portions
- **Cutaneous portion:** Epidermis and loosely arranged dermis with underlying muscle (orbicularis oculi) and scant adipose connective tissue
- Adnexal glands
  - ➢ Glands of Zeiss: Sebaceous glands with ducts opening into infundibula of the eyelashes
  - ➢ Meibomian glands: Sebaceous glands in tarsus with ducts opening at the eyelid margin
  - ➢ Glands of Moll: Apocrine glands also opening into the infundibula of the eyelashes
- Tarsal muscles: Small bundles of smooth muscle within the upper eyelid (Müller muscle) and lower eyelid which help keep the eyelids open
- Levator palpebrae superioris is in the upper eyelid (striate muscle)
- **Conjunctival portion:** Has dense connective tissue containing meibomian glands (tarsus) and the palpebral conjunctiva
- Tarsus: Dense connective tissue immediately posterior to the muscles of the eyelid
- Accessory lacrimal glands
  - ➢ Wolfring (near the end of tarsus)
  - ➢ Krause (near the fornix)
- **Lacrimal drainage apparatus** is composed of the puncta, canaliculi, lacrimal sac, and nasolacrimal duct

Path Presenter

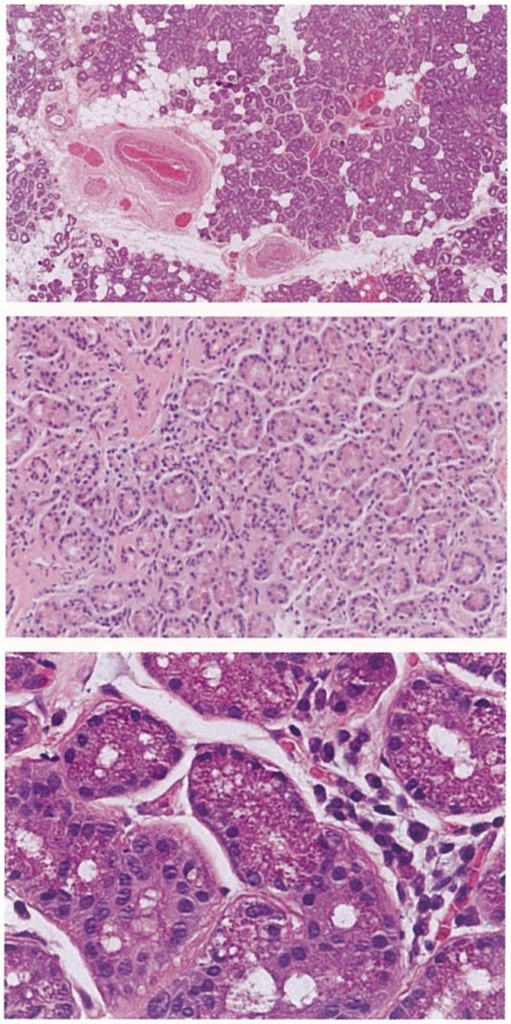
- Tear drain → medial canthus and through lacrimal puncta → lacrimal canaliculi → lacrimal sac → nasolacrimal duct → inferior nasal meatus



Sclera (H&E) showing a disorganized array of collagen bundles with few scattered fibroblasts

SCLERA

- Formed by interwoven bundles of collagen, predominantly type I, with a moderate amount of type II collagen
- The sclerocytes (fibroblasts) are scattered among the fibrous bundles
- The sclera is relatively avascular, with some branches from the anterior ciliary artery in the region of the Schlemm's canal
- The lens is required for normal growth and development
- Neural crest cells will differentiate into nasal sclera and uvea
- Temporal sclera is of mesodermal derivation



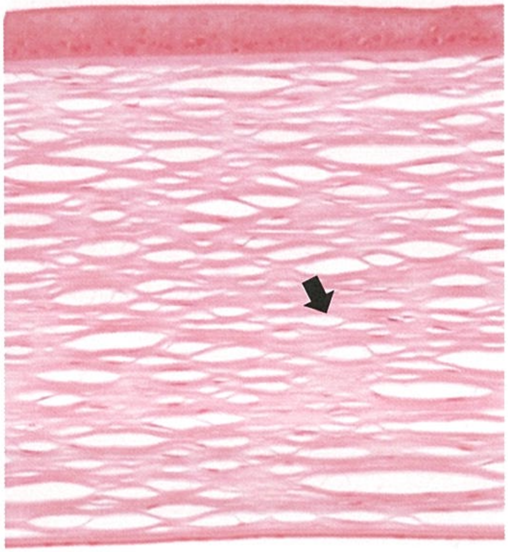
H&E showing acini of the lacrimal gland lined by columnar epithelial cells. Myoepithelial cells surround some acini. Scattered plasma cells and lymphocytes are normally present

ORBIT & LACRIMAL GLAND

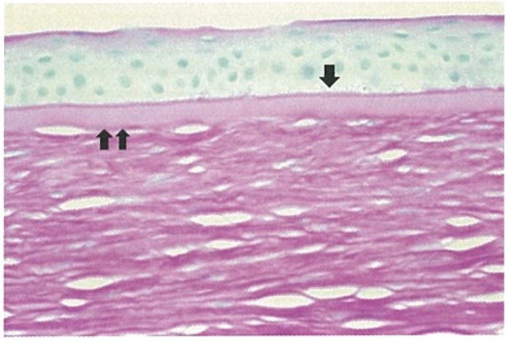
- The bones of the skull, face, and nose define the posterior and peripheral borders of the orbit
- The periosteum of the orbital bones gives rise to the orbital septum, a dense connective tissue sheet that extends into the eyelids
- Contents of the orbit
  - Globe
  - Optic nerve and meningeal covering
  - Tenon capsule
  - Extraocular muscles
  - Lacrimal gland
  - Blood vessels and fibroadipose connective tissue
  - Cranial nerves (oculomotor, trochlear, and abducens)
  - Branches of the ophthalmic division of the trigeminal nerve as well as sympathetic and parasympathetic innervation to the cornea, conjunctiva, iris, and muscles of the ciliary body
  - Arc-shaped trochlea (cartilaginous structure)
- Lacrimal gland in the superolateral aspect of the orbit is not encapsulated and is divided into a larger orbital lobe and a smaller palpebral lobe
- Types of glands
  - Predominantly serous with many PAS-positive secretory granules
  - Myoepithelial cells surround the acini and the intercalated ducts
  - Mucinous cells, similar to the ones in salivary glands, also appear in the ducts but rarely in the acini
- With aging, there is diffuse fibrosis of the lacrimal gland (orbital part in females and palpebral part in males), sometimes with periductal fibrosis
- The orbit lacks lymphoid tissue but contains scattered lymphocytes

Path Presenter

24. EYE PATHOLOGY

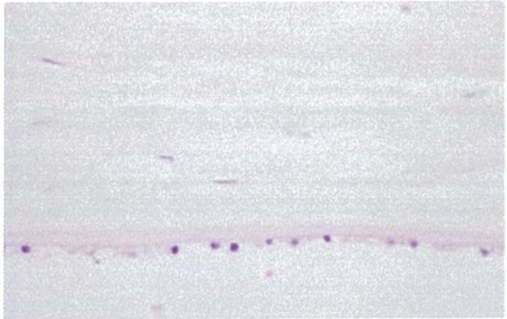


H&E showing cornea full thickness, 90% is stroma. Clefts seen amid the collagen lamellae (arrow) are an artifact of fixation



PAS stain shows corneal epithelium resting on a thin basal lamina (single arrow), hard to appreciate on H&E but easily seen on PAS;

Bowman layer (double arrows) underlies the basal lamina

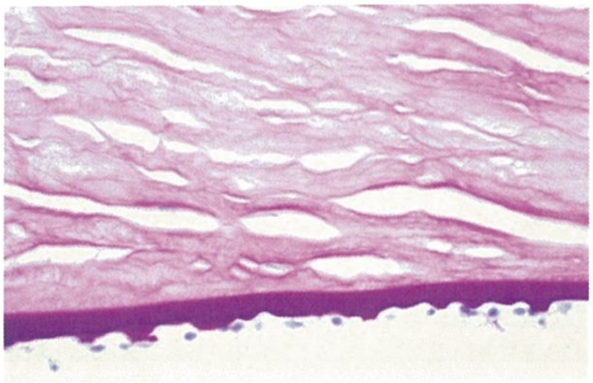


PAS stain shows the posterior surface of the Descemet membrane (double arrows) with a thin monolayer of corneal endothelial cells (single arrow)

Picture courtesy: Codrin E. Iacob, MD

CORNEA

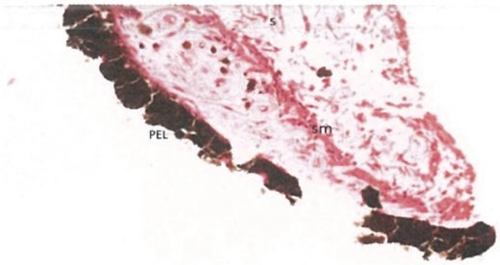
- Architecture: Corneal epithelium, basal lamina, Bowman layer, stroma, Descemet membrane, corneal endothelium
- 90% of the corneal thickness is stroma
    - **Stroma** is composed of parallel layers or lamellae of collagen in a proteoglycan extracellular matrix
    - Anterior stroma is less eosinophilic than the posterior stroma
    - Keratocytes are transformed fibroblasts within the stroma
- Normal cornea lacks blood vessels
- Nutrition to the cornea is provided by the arterial plexus in the cornea-sclera junction and by the contact of the aqueous humor of the anterior chamber
- **Descemet membrane: A true basement membrane**
    - Formed during fetal life; at birth 2-4 µm, in adults 10-12 µm
    - Important in corneal transplant: Descemet membrane is stripped from the host cornea and replaced by Descemet membrane with corneal endothelium from donor, with or without some posterior stroma (DSAEK and DMEK, respectively)
    - Descemet membrane thickens with aging. Excrescences on the peripheral portion of the Descemet membrane, known as peripheral guttae or Hassall-Henle warts (see picture below), represent an aging change



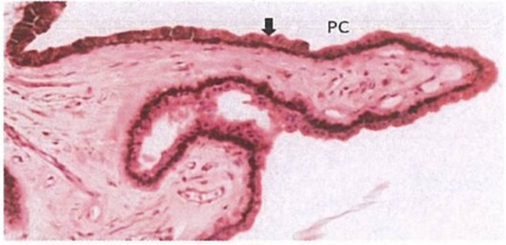
Picture courtesy: Codrin E. Iacob, MD

- The corneal endothelium is directly exposed to the aqueous humor in the anterior chamber. There are no real vessels, but the term "endothelium" is historical in corneal literature
- The corneal endothelial cells are osmotic pumps that preserve the corneal clarity in states of stromal dehydration
- Endothelial decompensation results in corneal loss of transparency
- The endothelial cells are positive for S100, suggesting neural crest origin
- **The cornea is well innervated**
    - 20% of corneal nerves are linked to mechanoreceptors
    - 70% are polymodal nociceptors and can respond to chemicals, extreme temperature, and inflammatory mediators
    - 10% are cold sensitive

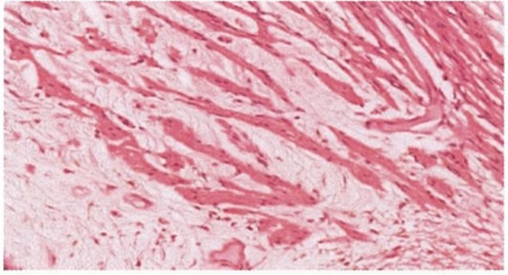
24. EYE PATHOLOGY



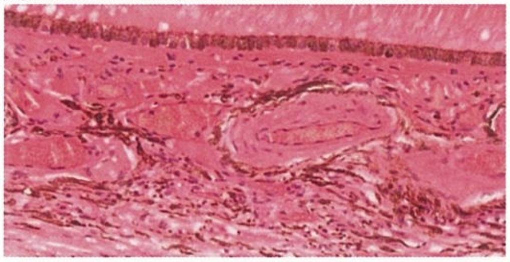
H&E showing iris with stroma (S), sphincter muscle (SM), and posterior epithelial lining (PEL)



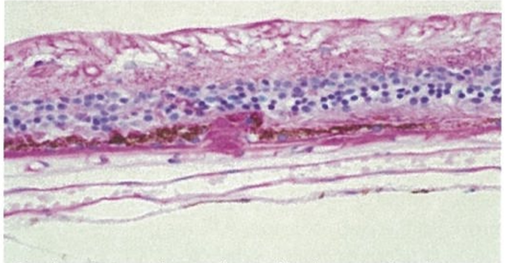
H&E showing the posterior chamber (PC) is in contact with the inner non-pigmented cells of the ciliary body (single arrow), while the stroma is in contact with the outer pigmented cells



H&E showing smooth muscle of the ciliary body with pigmented melanocytes in between muscle bundles



H&E showing vascularized choroid

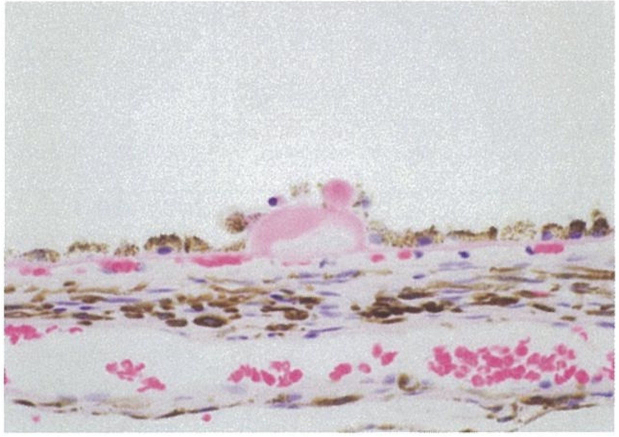


H&E showing Bruch membrane (BM) separating the choroid from the retinal pigment epithelium; an excrescence (drusen) is marked

UVEAL TRACT

- The uveal tract is located between the outer sclera and the retina and is composed of iris (anterior), ciliary body, and choroid (posterior)
- It was thought to resemble the dark color of a grape (uvea)
- **Iris**
  - Composed of stroma and posterior pigmented epithelial lining
  - Smooth muscles (sphincter and radial muscles) adjust pupil diameter
  - Stromal melanocytes give iris color
- **Ciliary body**
  - The epithelium has 2 layers: Internal non-pigmented and external pigmented layers
  - The pars plicata of the ciliary body produces the aqueous fluid
  - The ciliary muscle assists in lens accommodation
- **Choroid**
  - Vascularized, extends from the ciliary body to the optic nerve
  - Bruch membrane separates the choroid from the inner retinal pigment epithelium (RPE)
  - With aging, the Bruch membrane gets thicker and may acquire excrescences (drusen), which can calcify
- Drusen
  - Drusen are focal or diffuse basement membrane products from the RPE
  - As they transit in the choriocapillaris, other material might get trapped within the drusen, resulting in different types

  - **Nodular drusen (hard)** are mostly congenital, eosinophilic, positive for PAS, amorphous appearance, and the overlying RPE is usually atrophic and the adjacent one hypertrophic. Poor correlation to age-related macular degeneration
  - **Large drusen (soft)** are subdivided into dry (atrophic) and exudative (wet); significant risk factor for the development of dry (atrophic) or exudative (wet) age-related macular dystrophy (ARMD)
  - When macular atrophy is extensive, there is association between glaucoma and family history of ARMD, female >> male
  - Drusen changes can also be seen in choroid, where the deposits lie in between the veins (reticular pattern seen in clinic)
  - Deposits contain Iba1-immunoreactive immune cells and are positive for vibronectin while negative for lipid stain (oil red O)
  - Drusenoid RPE detachments can precede geographic atrophy of the RPE

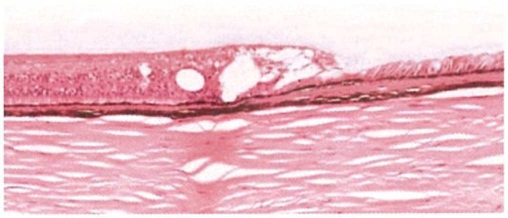


H&E showing drusen
Picture courtesy: Codrin E. Iacob, MD

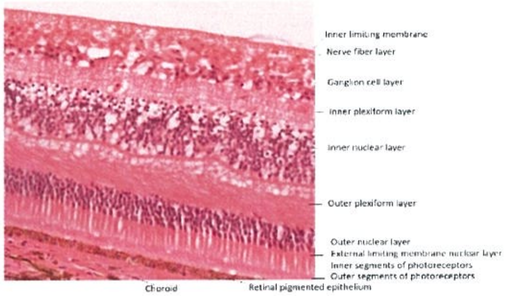
24. EYE PATHOLOGY

RETINA

- The choroid is outer to the retinal pigment epithelium which lies on Bruch membrane
- Outer and inner segments of the photoreceptors are located immediately adjacent to the RPE
- Photoreceptor cell bodies are in the outer nuclear layer
- Synapses involving bipolar cells and the photoreceptors, as well as horizontal cells, occur in the outer plexiform layer
- The inner nuclear layer (reactive to NeuN) encompasses the nuclei of the amacrine (intrinsic interneurons), bipolar, horizontal, and Müller cells (glial)
- The inner plexiform layer contains axons and dendrites of bipolar, amacrine, and ganglion cells
- Ganglion cell bodies are in the ganglion cell layer (synaptophysin positive and NeuN positive)
- The nerve fiber layer collects all the axons from retinal ganglion cells
- Inner limiting membrane: Structural boundary between the retina and the vitreous humor
- GFAP highlights retinal glial processes
- Müller cells can cause retinal gliosis in response to injury
- The central retinal artery supplies the inner nuclear, inner plexiform, and ganglion layers. Thus, central retinal occlusion will affect those layers



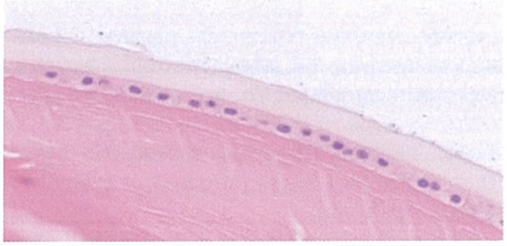
Ora serrata on H&E shows the monolayer, non-pigmented ciliary body epithelium converging with the multilayered retina


Inner limiting membrane
Nerve fiber layer
Ganglion cell layer
Inner plexiform layer
Inner nuclear layer
Outer plexiform layer
Outer nuclear layer
External limiting membrane nuclear layer
Inner segments of photoreceptors
Outer segments of photoreceptors
Choroid
Retinal pigmented epithelium

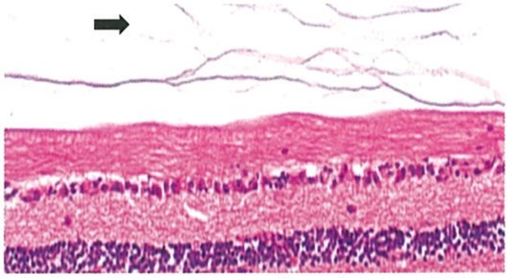
H&E showing retina layers

LENS

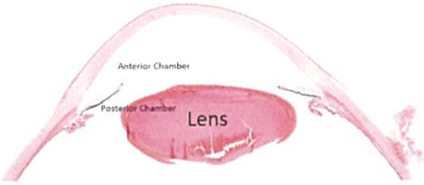
- An eosinophilic, acellular band (lens capsule) lies external to a single cuboidal epithelial cell layer in the anterior lens
- The lens capsule has abundant carbohydrate and reacts with PAS
- The posterior lens capsule is thinner than the anterior one and is devoid of epithelial cells
- Lens cortex is normally transparent but opacifies with aging (cataract)
- The anterior chamber is delimited anteriorly by the cornea and posteriorly by the iris and pupil
- Anterior chamber is filled with aqueous humor
- The vitreous humor extends from the neurosensory retina to the lens and is comprised of gel-like matrix with some collagen fibrils (mesenchymal tissue) and rare hyalocytes



H&E of lens showing eosinophilic, acellular band above a single epithelial cell layer

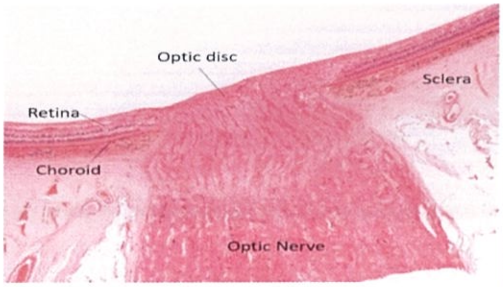


H&E shows the vitreous humor (arrow) as an acellular amorphous material


Anterior Chamber
Posterior Chamber
Lens

OPTIC NERVE

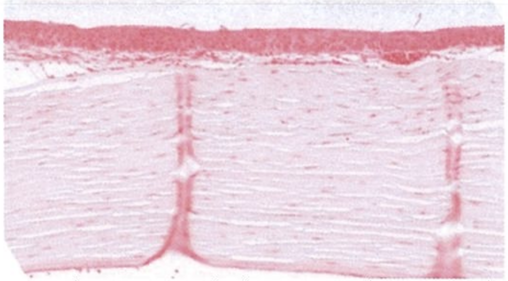
- The optic nerve is surrounded by pia, arachnoid, and dura mater; meningothelial cells in the arachnoid have associated psammoma bodies
- From the optic nerve head, the axons travel through the slit-like openings within lamina cribrosa; the post-laminar axons are myelinated
- Pigmented melanocytes are seen within the leptomeninges
- The optic nerve travels posteriorly to the optic foramen (25 mm)
- Nasal fibers cross through chiasm, then continue in optic tracts
- Temporal nerve fibers continue uncrossed into optic tracts
- With age, corpora amylacea can be seen in the optic nerve

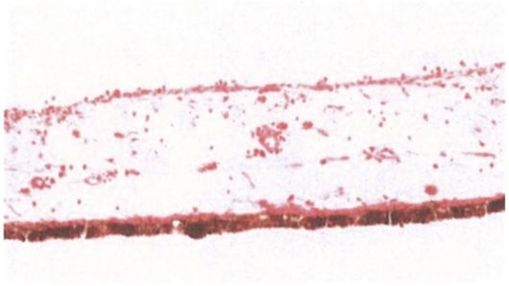

Optic disc
Sclera
Retina
Choroid
Optic Nerve

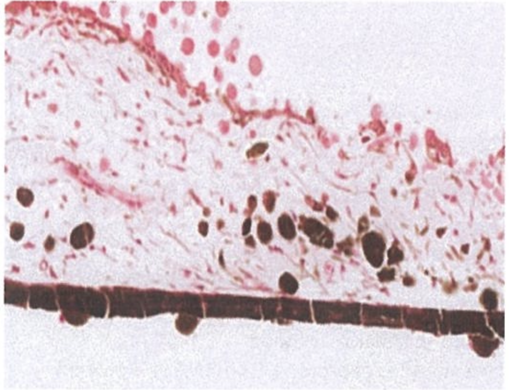
H&E showing optic nerve

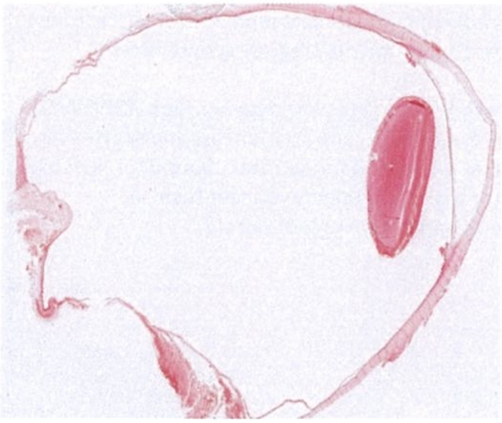
24. EYE PATHOLOGY

GLAUCOMA


H&E showing corneal changes in glaucoma with subepithelial vascularization, edema, and bullae characterizing degenerative subepithelial panus


H&E showing iris with atrophic stroma


H&E showing pigment dispersion in the iris


Early stage secondary open angle glaucoma

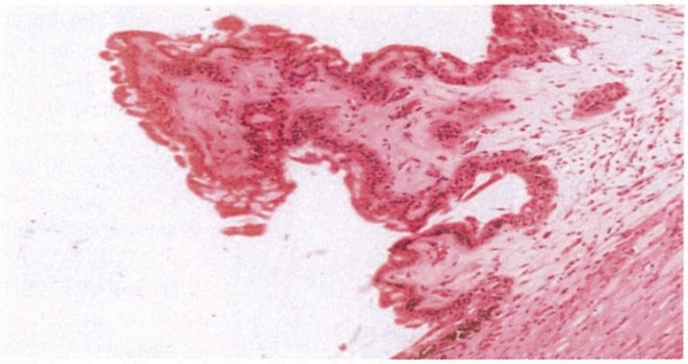
GLAUCOMA

MORPHOLOGY

- Tissue changes due to elevated intraocular pressure
  - Cornea: Edema of stroma and epithelium, epithelial bullae, corneal ulcer, degenerative subepithelial pannus, irregular basement membrane, atrophy of epithelium and endothelium, corneal neovascularization
  - Anterior-chamber angle: Scarring from chronic glaucoma
  - Iris: Dispersion of pigment, fibrosis of stroma, atrophy of the stroma muscle, necrosis of the stroma muscle, ectropion uveae due to neovascularization of the iris; hyperpigmentation can happen with topical prostaglandin therapy
  - Ciliary body: Fibrosis and hyalinization in the ciliary processes of the pars plicata, as well as atrophy
  - Lens: Cataract (especially after surgery for glaucoma)
  - Sclera: Ectasia, thinning, staphyloma (circumscribed outpouching of the wall of the globe)
  - Neural retina: Ganglion loss and nerve fiber layer thinning
  - Optic nerve head: Cupping (with or without reactive gliosis) **demonstrated by H&E below**, accelerated drop in nerve fibers (atrophy/loss of nerve fibers)

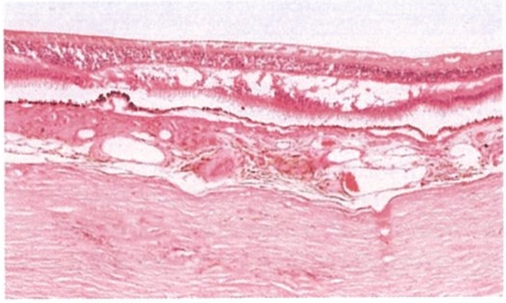
HIGH YIELD POINTS

- Leading cause of blindness (accounts for 1 out of 7 blind people in the U.S.)
- Glaucoma affects 0.5-1% of general population
- Subtypes
  - **Primary open-angle glaucoma (POAG):** Accounts for 2/3 of glaucoma in white people (includes normal tension glaucoma [NTG])
  - **Primary angle-closure glaucoma (PACG):** Most patients are in Asia
  - **Secondary angle-closure glaucoma:** Repeated PACG → synechia/trabecular damage; subluxated or anterior dislocated lens or surgical or non-surgical trauma → pupillary block → peripheral anterior synechia; dense vitreous hemorrhage (anterior displacement of the lens), uveal melanoma, neovascularization of the surface of the iris, juvenile xanthogranuloma
  - **Secondary open-angle glaucoma** → secondary to cells and debris in angle (hyphema, uveitis, etc.)
  - **Congenital glaucoma (impaired outflow):** Autosomal recessive (primary congenital) or infectious-related (congenital rubella/Zika virus infection)

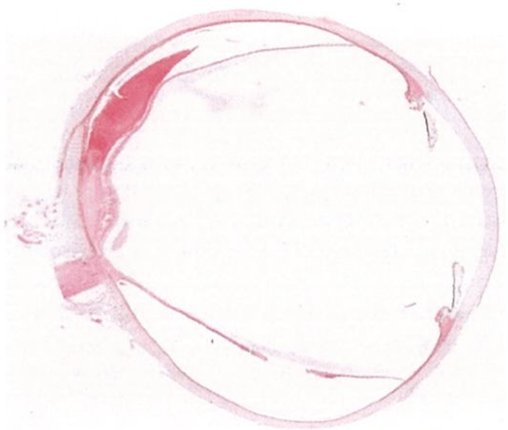

H&E showing ciliary body fibrosis, hyalinization

Path Presenter

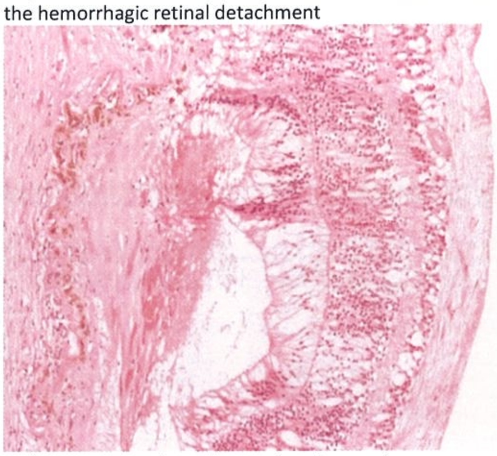
MACULAR DEGENERATION



H&E of dry ARMD showing irregular degeneration of the RPE with areas of increased translucency and pigment loss. Degeneration of the outer retinal layers, cystic changes in the outer plexiform layer. Bruch membrane might be thickened. Photoreceptors and inner nuclear cells can decrease (apoptosis). Macrocystoid retina (retinoschisis) and hole formation can occur in the wall of the macrocyst



H&E showing exudative, wet, or senile disciform macular degeneration (Kuhnt-Junius macular degeneration). Note the hemorrhagic retinal detachment



High-power view from the previous image shows organized scar tissue and subretinal neovascularization resulting in hemorrhage, fibroplasia, and complete degeneration of the photoreceptors

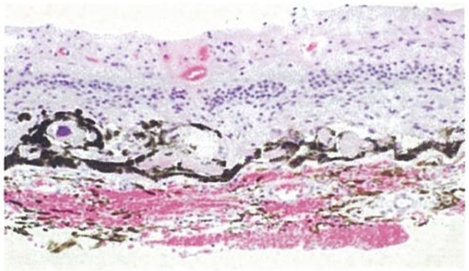
AGE-RELATED MACULAR DEGENERATION (ARMD)

MORPHOLOGY AND OTHER HIGH YIELD POINTS

- **Most common form of irreversible vision loss in the U.S.**
- Cause is unknown, but literature on genetic factors is extensive
- May be related to vascular proliferation in the choriocapillaris and retinal pigment epithelium
- Risk increases with age (especially > 75 years old)
- Other risk factors: High cholesterol, exposure to sunlight, soft and hard drusen, blue iris color, vitreoretinal traction, cataract surgery, and small globe
- Retinal damage is mainly in the **fovea-macular area**
- 2 most important types

Non-disciform (atrophic or dry type) – gradual vision loss

- The RPE atrophy spread and form geographic atrophy
- The atrophic areas follow the flattening of soft drusen
- RPE detachment can occur
- Retinal changes are often bilateral



H&E showing dry ARMD with numerous dry drusen, including one calcified interruption of the RPE layer with zonal loss of photoreceptors

Picture courtesy: Codrin E. Iacob, MD

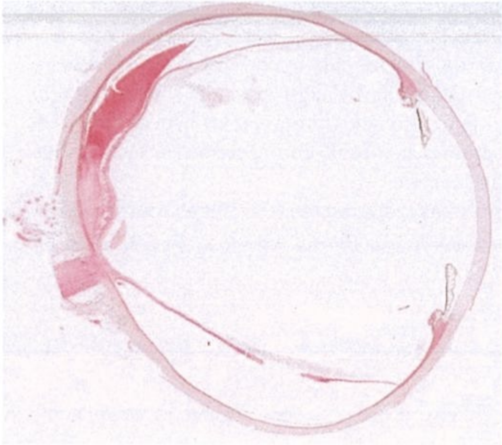
Disciform (wet or exudative) – sudden vision loss

- **Most common cause of legal blindness**
- Can happen after non-disciform
- Hemorrhagic retinal detachment secondary to neovascularization
- Vessels from the choriocapillaris penetrate through Bruch membrane and leak fluid which organizes into macular scar tissue
- Sub-foveal fibrovascular membranes express VEGF mRNA and protein
- Pathologic process is similar to granulation tissue associated with diffuse soft drusen
- Idiopathic subretinal (choroidal) neovascularization can occur regardless of any disorder in younger people and may regress spontaneously

- Other relevant types
  - **Congenital hypotrichosis with juvenile macular degeneration (CHWJMD):** Rare, occurs in childhood, presents with central vision loss and sparse hair
  - **Exudative macular degeneration secondary to focal choroiditis** (juvenile disciform degeneration of the macula): Patients younger than 50, secondary to inflammatory cell infiltration of the choroid

Path Presenter

24. EYE PATHOLOGY



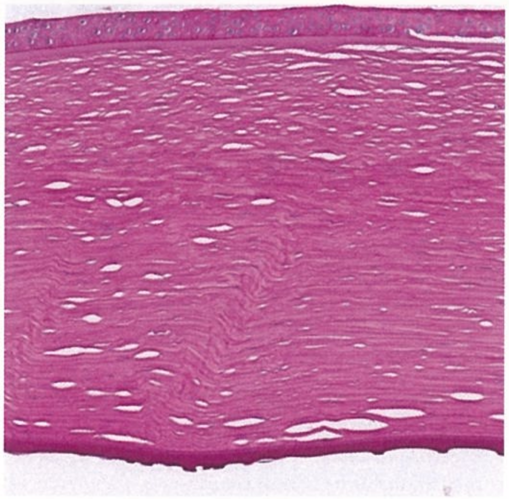
Path Presenter

NEURAL RETINAL DETACHMENT

MORPHOLOGY AND OTHER HIGH YIELD POINTS

- Separation of the photoreceptor layer from the RPE
- Major causes
  - Accumulation of fluid beneath an intact retina (Coats disease, malignant hypertension, eclampsia, subneural retinal hemorrhages, choroidal [uveal] malignant melanomas)
  - Traction bands in the vitreous humor due to diabetes, vitreous bands, post-traumatic vitreous humor fibrosis, complications after cataract surgery
  - Rhegmatogenous neural retinal detachment: fluid accumulation in a broken retina with vitreous band traction
- Classification
  - **Rhegmatogenous**
    - Equatorial type: Related to myopia, lattice degeneration, uveitis (50 years old)
    - Oral type (ora serrata): Aphakia (before the era of extracapsular cataract extraction), traumatic
    - Macular type: High myopia, traumatic involving the macula
  - **Non-rhegmatogenous**
    - Transudative: Uveitis, scleritis
    - Exudative: Choroidal tumor (75% of uveal melanomas)
    - Hemorrhagic: Eclampsia, Goodpasture syndrome, post-traumatic)

CORNEAL DYSTROPHY



PAS stain showing cornea with Fuchs dystrophy and characteristic wart-like bumps present in the Descemet membrane

CORNEAL DYSTROPHIES MORPHOLOGY OVERVIEW

- Dystrophies are primary, bilateral, and usually inherited
- Classification is evolving (International Classification of Corneal Dystrophies [IC3D]). Each main category has several subcategories
- Main categories/classification IC3D 2015
  - Epithelial-stromal TGFB1 dystrophies (includes lattice and granular; also stromal includes mucopolysaccharidoses and mucolipidoses)
  - Bowman layer dystrophies
  - Stromal dystrophies
  - Descemet membrane and endothelial dystrophies (which contain the Fuchs endothelial corneal dystrophy [FECD])

FUCHS DYSTROPHY

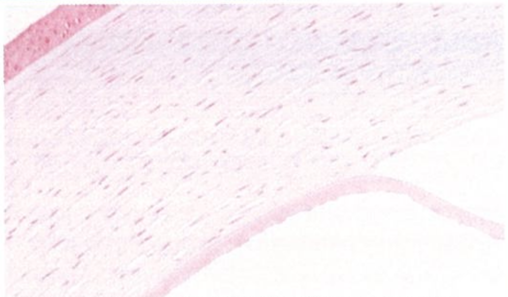
MORPHOLOGY AND OTHER HIGH YIELD POINTS

- In 1910, Ernest Fuchs described **cornea guttata**
- Fuchs dystrophy is the most common endothelial corneal dystrophy responsible for **50% of all corneal transplants** in developed countries
- FECD: Has several variants (FECD1-7), most with age of onset in the 4th decade or later, but one early variant FECD1 starts in the 1st decade
  - Mode of inheritance: FECD1 and FECD3 are autosomal dominant, FECD2 unknown, some are sporadic
  - Gene in FECD1: Col8A2 (alpha chain of collagen type VIII)
  - A trinucleotide repeat (CTG) was found in Caucasians, which results in expansion of transcription factor 4 (TCF4)
  - Significant downregulation of ion transporters results in compromised corneal endothelial pump function
- **4 stages clinically and histologically**
  - **Asymptomatic:** Excrescences resembling Hassall-Henle warts are present centrally; Descemet membrane electron microscopy shows foci of abnormal structure and evidence of hyperproduction
  - **Stage of painless decrease of vision, glare:** Mild stromal and intraepithelial edema involving the basal layer followed by superficial stroma through

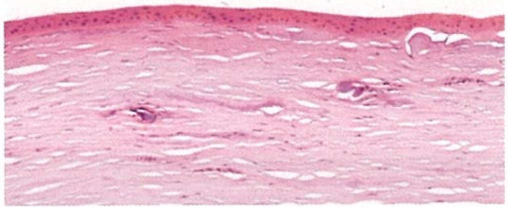
Bowman membrane with production of subepithelial fibrous membrane as a degenerative pannus (variable thickness)

- **Stage of periodic pain:** Marked stromal edema and intraepithelial edema that leads to bullae (bullous keratopathy) with periodic ruptures (pain). Atrophy of the corneal epithelium mixed with areas of hypertrophy. The basement membrane formation is increased. Complications include corneal infection, ulceration, and perforation
- **Stage of no pain but vision severely decreased:** Degenerative pannus thickens, and this scar results in decreased vision. Late complication includes glaucoma

Path Presenter Path Presenter


H&E showing another example of cornea with Fuchs dystrophy and characteristic wart-like bumps present in the Descemet membrane

LATTICE DYSTROPHY


H&E showing stromal deposits of amyloid

MORPHOLOGY

- Irregular subepithelial and stromal deposits of amyloid (birefringent with Congo red)
- Normal Descemet membrane and endothelium

HIGH YIELD POINTS

- Subtypes (I-III); most are autosomal dominant
- Type II is associated with familial amyloid polyneuropathy (amyloid derived from mutated gelsolin)

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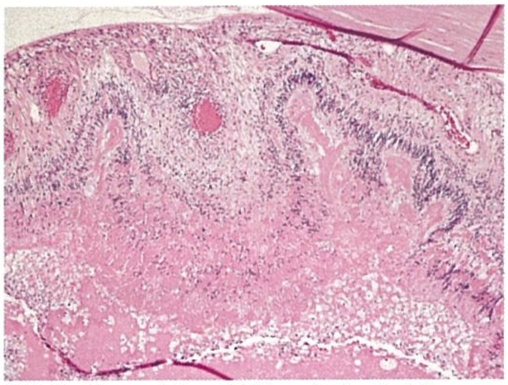
COATS DISEASE


H&E showing exudative retinitis and telangiectatic vessels in Coats disease
Open-source image: AFIP

COATS DISEASE

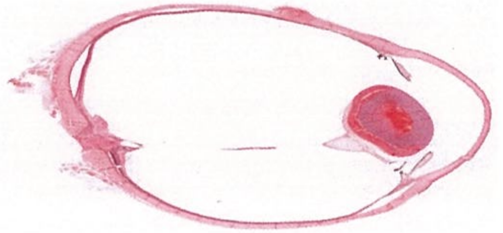
MORPHOLOGY

- Idiopathic retinal telangiectasis with exudation can be severe, focal juxtafoveal, or associated with other diseases (bilateral Coats may be associated with CRB1-associated retinal dystrophy, familial exudative vitreoretinopathy)

HIGH YIELD POINTS

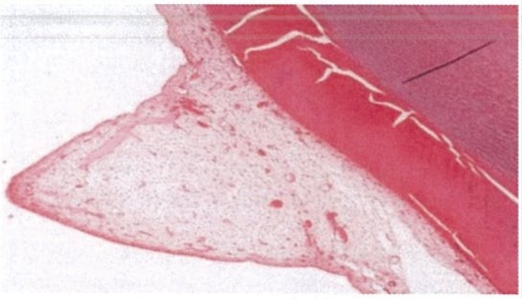
- Classification (typical and atypical)
- Coats disease is a congenital, non-hereditary, sporadic condition
- Coats disease is the most common lesion simulating retinoblastoma
- Mostly unilateral, rarely bilateral
- Mainly affects boys (18 months to 18 years), mean age 6 (older age than retinoblastoma); younger age associated with worse prognosis
- Can present as asymptomatic or with decreased vision, strabismus, and leukocoria; neovascular glaucoma can occur in 10% of cases
- Coats plus syndrome: Bilateral Coats + cerebral calcifications + leukoencephalopathy + defects of bone marrow

PERSISTENT HYPERPLASTIC PRIMARY VITREOUS


H&E showing persistent hyperplastic primary vitreous (note the combined anterior and posterior PFV); in the equatorial region, there is a remnant of the hyaloid artery

PERSISTENT FETAL VASCULATURE

- Persistent fetal vasculature (PFV) has mostly replaced the term persistent hyperplastic vitreous
- 5% of childhood blindness
- Associated with white reflex behind pupil (leukocoria)
- Can simulate retinoblastoma, mostly unilateral, rarely bilateral
- Congenital anomaly: Remnant of the primitive hyaloid vascular system
- Sometimes the entire hyaloid vessel from the optic disc to the back of the lens may remain
- **Anterior PFV:** Anterior to the original vitreous artery, remains integrated with the posterior capsule (retrolens). Associated features include microphthalmia, shallow anterior chamber, lens opacity, and glaucoma



H&E showing dense fibrovascular retrolens mass

- **Posterior PFV:** Preretinal membranes, vitreous stalk, optic hypoplasia, and retinal detachment
- **Combined** (anterior and posterior)

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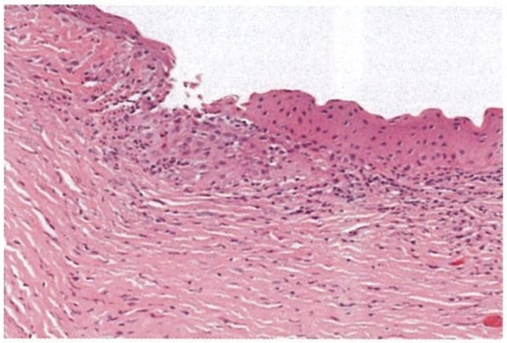
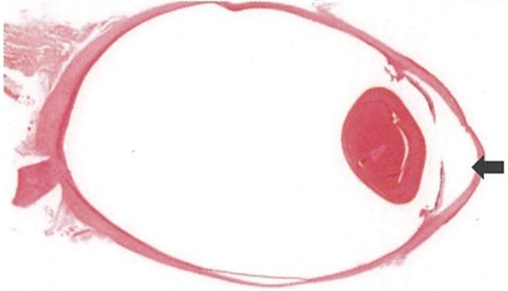
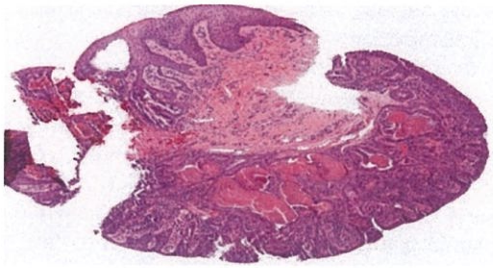
INFLAMMATIONS OF THE EYE AND ORBIT



H&E shows acute and chronic nongranulomatous inflammation and a corneal ulcer characterizing keratitis. Intranuclear inclusions may or may not be seen, and PCR for HSV or HSV ISH confirms the diagnosis of HSV keratitis



H&E shows corneal scarring in a patient with long history of herpetic keratouveitis



H&E shows chronic conjunctivitis; islet of epithelium may form retention cysts that can calcify

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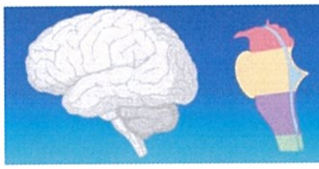
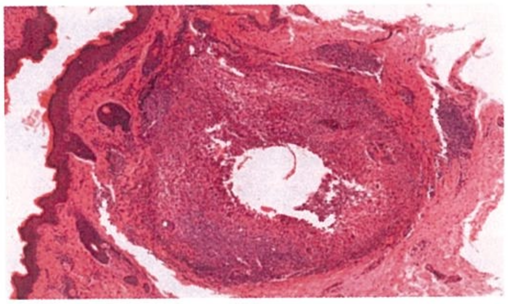
NONGRANULOMATOUS INFLAMMATION

- Classification according to the tissue: Cornea (keratitis), retina (retinitis), uvea (uveitis)
- Terminology:
  - **Endophthalmitis:** One or more coats of the eye (vitritis) and adjacent cavities are inflamed
  - **Panophthalmitis:** All 3 coats of the eye (sclera, choroid, retina) show inflammation, may spread to the orbit
  - Exogenous: External agents (trauma, allergy, chemical exposure)
  - Endogenous: Hematogeneous spread (virus/bacteria), contiguous spread (sinusitis); inflammation due to secondary cellular immunity like phacoantigenic endophthalmitis, Behçet disease (chronic endophthalmitis)
- **Acute suppurative:** Predominant polymorphonuclear (PMN) leukocytes (pus) usually secondary to bacteria (S. aureus), also due to Behçet disease
- **Nonsuppurative examples:** Cellulitis secondary to S. hemolyticus, acute (PMN) or chronic uveitis (plasma cells), acute or chronic keratitis due to HSV, EBV, Zika virus, rubella; neonatal cases with differential TORCH syndrome (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex)
  - Myxoviruses can cause acute retinitis in the setting of subacute sclerosing panencephalitis (SSPE)
- Systemic conditions: HLA-B27-related such as Reiter (conjunctivitis or iridocyclitis) and ankylosing spondylitis (uveitis); Behçet disease, Kawasaki disease, rheumatoid arthritis, Still disease, and juvenile rheumatoid arthritis (uveitis in children), Crohn's disease (acute episcleritis, acute anterior uveitis, and less commonly conjunctivitis, optic neuritis, and retinal vasculitis), and systemic lupus erythematosus (uveitis, rare)
- **Sequelae of uveitis, endophthalmitis, and panophthalmitis**
  - Corneal endothelial degeneration or **glaucoma**
  - Secondary infections due to ruptured corneal bullae
  - Calcium deposits beneath the corneal epithelium, band keratopathy (Still disease)
  - Corneal vascularization, scarring
  - Organized inflammation → scar → obliterate the angle of the anterior chamber
  - Iris may show atrophy, neovascularization → anterior chamber angle synechia → closure → glaucoma
  - Chronic anterior uveitis → synechia formation
  - **Subcapsular cataract:** Anterior if iritis or iridocyclitis, posterior if intraocular inflammation induces lens epithelium to migrate posteriorly
  - Ciliary body may become flattened/fibrosed or may proliferate, organizing fibrosis behind the lens
  - Between the vitreous humor and the retina neovascularization
  - Choroid may show scarring; chorioretinitis can destroy the Bruch membrane and RPE; choroid may fuse with retina

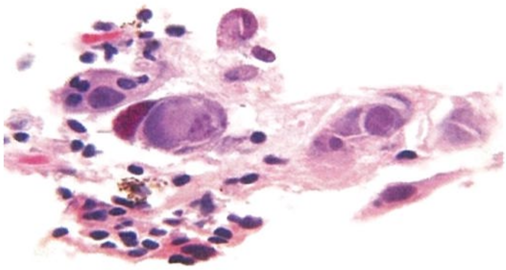


- Retina: Inflammation anywhere in the eye may cause perivascular inflammation in the retina
- **End stage of diffuse ocular diseases:** Atrophy with or without shrinkage and disorganization, eventually intraocular ossification

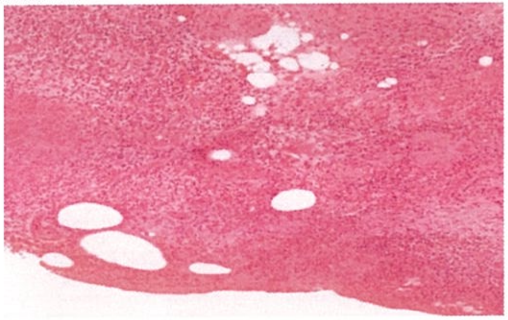
H&E of the eyelid shows a granulomatous nodule with central necrosis. The patient was treated for Loa loa with a cycle of banocide



H&E showing CMV retinitis
Picture courtesy: Codrin E. Iacob, MD



H&E showing lipogranulomatous changes, typical of chalazion



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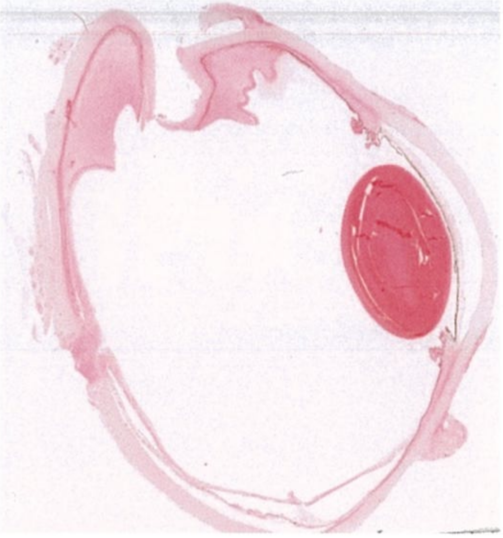
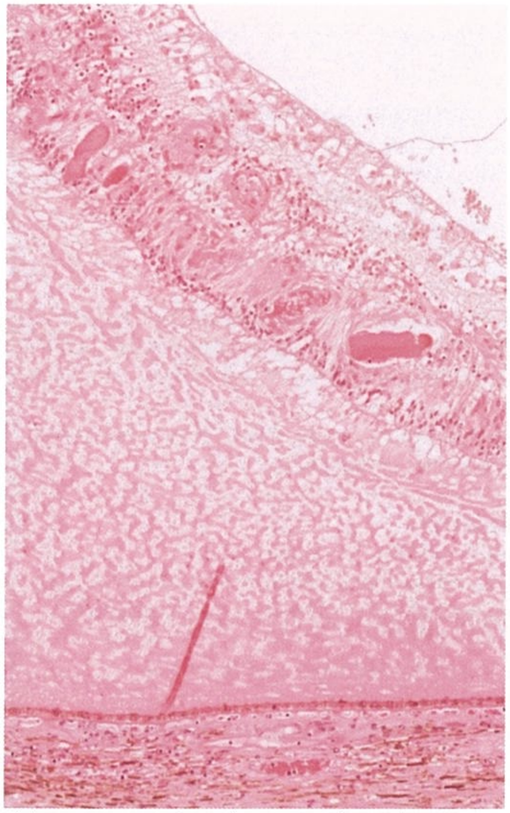
GRANULOMATOUS INFLAMMATION

- Sympathetic uveitis (sympathetic ophthalmia [SO]) → bilateral, granulomatous, T-cell-mediated uveitis occurring from 2 weeks to many years after a penetrating trauma
- Phacoantigenic endophthalmitis: Occurs when there is lack of tolerance to the lens protein → zonal granulomatous inflammation on a lens rupture
- Foreign body granulomas
- Tuberculosis and leprosy
- Syphilis (Treponema pallidum): Tertiary stage (gummas) - focal granulomatous vascular disease can affect any organ. Alternatively, can present as a nongranulomatous, posterior, chronic, indolent uveitis
- Lyme disease (Borrelia burgdorferi): Clinical stage 3 can present with ocular findings (stromal keratitis, episcleritis, cortical blindness, and even orbital myositis)
- Cat-scratch disease (Bartonella henselae): Can cause Parinaud oculoglandular fever, neuroretinitis, focal choroiditis with retinal detachment, optic nerve inflammation. Warthin-Starry silver stain can show the bacillus
- Tularemia (Francisella tularensis): Parinaud oculoglandular syndrome (conjunctivitis, pre-auricular lymphadenopathy with suppuration)
- Rhinoscleroma (Klebsiella rhinoscleromatis): Chronic destructive granulomatous disease affects nose, pharynx, larynx, nasolacrimal duct, lacrimal sac, orbit
- Fungi: Blastomyces, Cryptococcus, Coccidioides, Aspergillus, Rhinosporidium, Basidiobolus (phycomycosis), Mucorales, Candida, Sporothrix, Pneumocystis jiroveci. Sporothrix and Actinomyces: Affects lacrimal sac and may present as chronic conjunctivitis
- Toxoplasma gondii invades retinal cells, directly causing focal retinitis and overlying vitritis. When the lesion clears centrally, it destroys most of the retina and the choroid becomes pigmented and atrophic
- Malaria: Patients can present with retinal hemorrhage, keratitis, optic neuritis, peripapillary edema, or temporary loss of vision
- Virus: CMV, VZV (ophthalmic branch of the trigeminal nerve)
- **Nematodes, toxocariasis** (Toxocara canis): Usually infects children (< 11 years) with a puppy (not an adult dog). Can cause leukocoria and retinal folds that radiate out where the necrotic worm is located with painless ophthalmitis. Granulomatous inflammation with abundant eosinophils
- **Loa loa: Filarial worm** that invades the subcutaneous tissues and may land in the periorbital tissues, eyelids, and conjunctiva; can cause abscess formation; the organism is visible to the naked eye
- Non-traumatic and noninfectious: Sarcoidosis (anterior granulomatous uveitis in 20% of patients); granulomatous scleritis (rheumatoid arthritis-related), xanthogranulomas (Langerhans histiocytosis, juvenile xanthogranuloma, Chediak-Higashi syndrome, granulomatous reaction to Descemet membrane [10% of patients with corneal ulcer or keratitis])
- **Chalazion:** Chronic inflammation of meibomian glands or Zeiss glands
- Vogt-Koyanagi-Harada syndrome (uveomeningoencephalitic syndrome, VKH): Severe, acute, bilateral anterior uveitis associated with vitiligo, poliosis (whitened hair), alopecia, and dysacusia
- Harada's disease: Posterior granulomatous uveitis, bilateral, with retinal detachment and meningeal symptoms (CSF with increased protein levels)



H&E shows proliferative diabetic retinopathy in a patient with long-standing history of diabetes



Higher-power view from the previous figure showing retinal neovascularization and retinal detachment

DIABETIC RETINOPATHY (DR)

MORPHOLOGY

- All elements/levels of the retina undergo alterations: Vascular (altered tight junctions, endothelial cell damage, and pericyte death), glial (altered contact with vessels, release of inflammatory mediators, impaired glutamate metabolism), microglial (increased number, release of inflammatory mediators), neuronal (death of ganglion cells and inner nuclear layer, axonal atrophy)
- Exudative retinopathy: Hard or waxy exudates (serum and glioneuronal breakdown products)
- Macular edema: Fluid leaks out of the retinal vessels and enters Müller cells, resulting in intracellular edema (reversible with laser photocoagulation). Ballooning and death of Müller cells can occur (irreversible), foveal ischemia can ultimately lead to vision loss
- **Proliferative diabetic retinopathy (PDR)** is a vascular response to hypoxic neural retinal environment (mediated by VEGF) with advanced glycation end products and macrophages
  - ➢ The vitreous humor is proangiogenic in PDR
  - ➢ Neovascularization is initially intraretinal but evolves to lie between the retina and vitreous humor
  - ➢ There is fibrous gliosis (retinitis proliferans) and shrinkage of the glial component often results in retinal detachment
  - ➢ Once blindness develops, the average life expectancy is less than 6 years

OTHER HIGH YIELD POINTS

- **Leading cause of blindness in the U.S.**
- Over 75% of blind patients with DR are female
- Correlates with how long the patient has been diabetic
- In DM type 1, it can present at the onset of the disease
- Progression to blindness is related to the presence of maculopathy and glycemic control (HbA1c level)
- There is low frequency of DR in secondary diabetes (pancreatectomy, hemochromatosis, acromegaly, Cushing disease, etc.), possibly due to a decreased long-term survival of those patients
- Diagnosis is clinical: Fundoscopic examination shows microvascular changes in the macular area, capillary microaneurysms
- Hemorrhagic retinopathy can occur
- Proliferative retinopathy clinical diagnosis: Increased retinal hemorrhages, cotton-wool spots, venous dilatation, venous bleeding, intraretinal microangiopathy
- Complex pathobiology in diabetes involves every aspect of the eye, which is beyond the scope of this book

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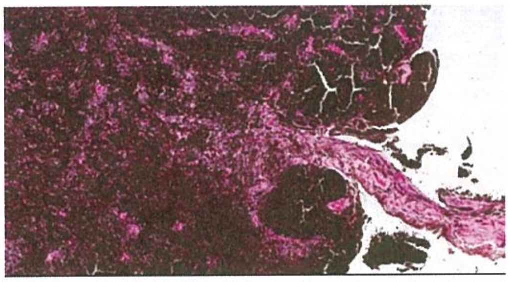
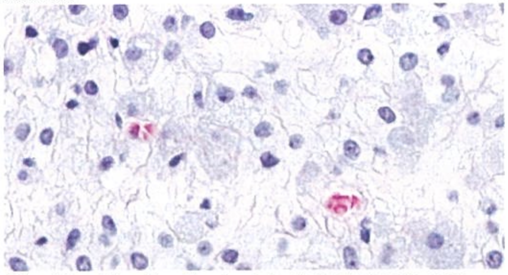
24. EYE PATHOLOGY

OCULAR AND ORBITAL TUMORS



H&E shows uveal melanocytoma characterized by polygonal cells with intracytoplasmic pigment; BAP1 retained



After bleaching, the bland cytologic features are seen

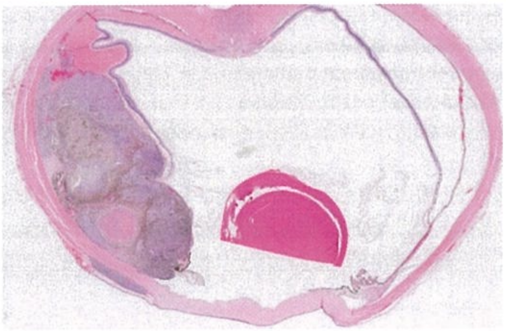
UVEAL MELANOCYTOMA (MAGNOCELLULAR NEVUS OF THE UVEA)

MORPHOLOGY

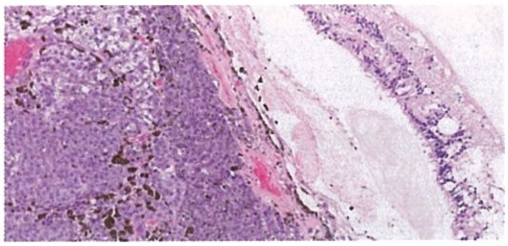
- Polygonal cells with intracytoplasmic melanin pigment
- More frequently in the iris and ciliary body than in the choroid, can also be found close to the optic nerve

OTHER HIGH YIELD POINTS

- Rare case reports of transformation into melanoma
- IHC: (+) SOX10, melan-A; BAP1 is retained
- Ki-67 is nearly zero
- GNAQ mutations are frequent
- Age of presentation varies (infants to elderly patients)



H&E showing melanoma cells extending from the choroid through the sclera and adjacent cornea at low power



High-power view of the melanoma cells arising from the choroid (uveal melanoma)

UVEAL MELANOMA

MORPHOLOGY

- Ciliary body melanomas are usually nodular, circumscribed
- Choroidal melanomas are dome-shaped, mushroom-shaped, or diffuse
- Spindle cell melanoma > 90% spindle cells
- Epithelioid melanoma > 90% tumor cells epithelioid
- Mixed cell melanomas: Variable spindle, epithelioid
- Choroidal and ciliary body melanomas are grouped by size:
    - Small (T1), medium (T2), large (T3), or very large (T4)
    - Subgrouped by (a) ciliary body involvement and extrascleral growth as choroid only; (b) ciliary body involved; (c) choroid and extrascleral < 5 mm; or ciliary body involved and extrascleral ≤ 5 mm (d), and extrascleral > 5 mm (e)
    - They are staged (stage I–IV) according to size, ciliary body involvement, extraocular extension, and presence of metastasis

OTHER HIGH YIELD POINTS

- Iritic, ciliary, or choroidal melanomas
- 25% asymptomatic; diagnosed in a routine eye exam
- Secondary glaucoma can happen when there is anterior displacement of lens-iris diaphragm, tumor seeding, iris neovascularization, tumor invasion of the iridocorneal angle
- IHC: (+) SOX10, S100; somatic/germline BAP1 loss in 50% of cases
- Poor prognostic factors: BAP1 loss, monosomy 3
- Mutations in GNAQ and GNA11 are helpful to distinguish uveal from other melanomas

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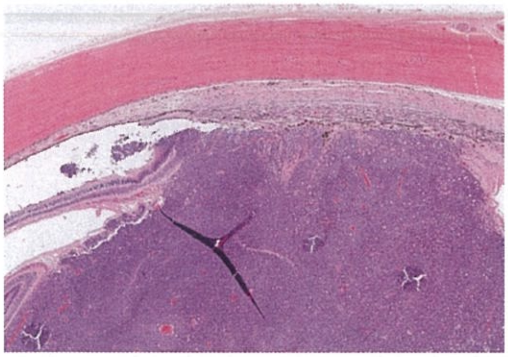
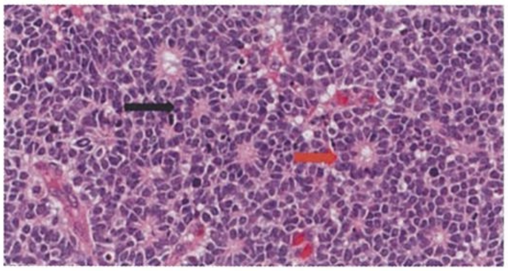
24. EYE PATHOLOGY



H&E low-power view of retinoblastoma



H&E showing Homer Wright rosettes, which contain a central tangle of neurofilamentary neuropil ringed by nuclei (black arrow) and Flexner-Wintersteiner rosettes, cells surrounding an empty lumen (red arrow) in retinoblastoma

RETINOBLASTOMA

MORPHOLOGY

- Tumor of the neurosensory retina that involves the vitreous
- Histology: Small round blue cell tumor with scant cytoplasm, frequent mitoses, rosettes, and necrosis (poorly differentiated retinoblasts)
- Exophytic white mass; 63% with leukocoria (white pupillary reflex)

OTHER HIGH YIELD POINTS

- Most common primary intra-ocular malignant tumor in children
- No sex or race predilection
- 80% are less than 3 years old
- 3.8% of patients with bilateral disease can also have an intracranial midline tumor (pineal gland or sella turcica) → trilateral retinoblastoma
- Advanced presentation can include glaucoma, buphthalmos, uveitis, orbital cellulitis
- Germline alteration of the RB1 gene
- Recently proposed subtypes: (1) later cone differentiation, not many genetic alterations; (2) MYC-amplified and BCOR-mutated tumors with less differentiation and ganglion neuronal genes
- High-risk features: Involvement of choroid, optic nerve, anterior structures
- IHC: (+) synaptophysin, NSE, Rb, SOX2; (-) CD99, GFAP, and leukocyte markers

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EYE & ORBIT TUMORS

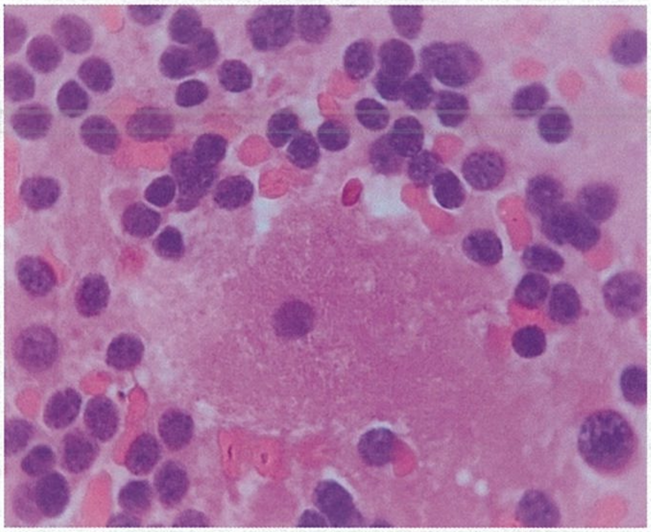
Skin and Eyelid	**Lacrimal Gland**	**Conjunctiva**
Basal cell carcinoma	Pleomorphic adenoma of the lacrimal gland	Conjunctival squamous cell papilloma
Squamous cell carcinoma	Lacrimal gland oncocytoma	Conjunctival oncocytoma
Merkel cell carcinoma	Myoepithelioma	Conjunctival squamous intraepithelial neoplasm
Ductal hidrocystoma	Intraductal carcinoma	Conjunctival squamous cell carcinoma
Syringoma	Carcinoma ex-pleomorphic adenoma	Adenosquamous carcinoma
Tubular adenoma	Adenoid cystic carcinoma	Junctional compound and subepithelial conjunctival nevi
Syringocystadenoma papilliferum	Primary ductal adenocarcinoma of the lacrimal gland	Blue nevus of the conjunctiva
Pilomatrixoma	Secretory carcinoma	Plexiform melanocytoma
Trichilemmoma	Mucoepidermoid carcinoma	Conjunctival melanocytic Intraepithelial lesion
Sebaceous carcinoma	Epithelial-myoepithelial carcinoma	Conjunctival melanoma
Adenoid cystic carcinoma	Acinic cell carcinoma	**Tumor-like Lesions of the Conjunctiva:**
Signet-ring cell/histiocytoid carcinoma	Adenocarcinoma NOS	Epithelial conjunctival inclusion cyst
Mucinous carcinoma	Lacrimal Drainage System	Reactive epithelial hyperplasia

Endocrine mucin-producing sweat gland carcinoma	Papilloma (squamous and inverted)	Papillary and follicular conjunctivitis
Microcystic adnexal carcinoma	Squamous cell carcinoma	Pterygium and pinguecula
Apocrine carcinoma	Lymphoepithelial carcinoma	Epibulbar choristoma (dermoid, dermolipoma, complex choristoma)
Nevi of the eyelid	Mucoepidermoid carcinoma	Epibulbar osseous choristoma
Spitz nevus	Melanoma involving the lacrimal drainage system	
In-situ cutaneous melanoma		
Invasive cutaneous melanoma		

Uveal Tract	**Retina**	**Optic Nerve and Optic Disc**
Benign hamartomas of the iris (Ectopic tissue, implantation cyst, pigmented epithelial cyst, Lisch nodule)	Astrocytic tumors (astrocytoma NOS, retinal astrocytic hamartomas-associated with TSC1 and TSC2 gene)	Optic disc choristoma (malformation)
Ocular melanocytosis	Nodular massive retinal gliosis	Gliomas of the optic nerve (pilocytic astrocytoma, pilomyxoid astrocytoma, diffuse gliomas including: astrocytoma, glioblastoma)
Iris nevus	Retinocytoma	Medulloepithelioma of the optic disc and optic nerve
Iris melanoma	Retinoblastoma	Meningioma of the optic nerve
Choroidal and ciliary body nevi	Hamartoma of the retinal pigment epithelium	Melanocytoma of the optic disc and optic nerve
Uveal melanocytoma	Congenital hypertrophy of the retinal pigment epithelium	
Bilateral diffuse uveal melanocytic proliferation	Reactive hyperplasia of the retinal pigmented epithelium	
Choroidal and ciliary body melanomas	Adenoma and adenocarcinoma of the retinal pigment epithelium	
Adenoma and adenocarcinoma of the ciliary body	Glioneuronal hamartoma of the ciliary body	
Medulloepithelioma of the ciliary body	Reactive hyperplasia of the ciliary epithelium	

Orbit	**Hematolymphoid**	**Soft Tissue and Bone Tumors**
Orbital desmoid tumors (choristomas and other cysts)	Reactive lymphoid hyperplasia	Fibroblastic tumors (fibrous histiocytoma, nodular and proliferative fasciitis, proliferative myositis, solitary fibrous tumor, dermatofibrosarcoma protuberans, angiomyxoma)
Cavernous vascular malformations	IgG4-related disease	Benign lipomatous tumor and Malignant adipocytic tumors
Combined lymphatic-venous malformation of the orbit	Primary choroidal lymphoma	Rhadbomyosarcomas
Orbital venous malformation	Primary vitreoretinal large B-cell lymphoma	Leiomyoma, mesectodermal leiomyoma, leiomyosarcoma
Arteriovenous malformation	Extranodal marginal zone lymphoma	Glomus tumor, myopericytoma, including myofibroma
Hamartoma (orbital glial heterotopia)	Follicular lymphoma	Peripheral nerve sheath tumors (Schwannoma, neurofibroma, solitary circumscribed neuroma, granular cell tumor, malignant peripheral nerve sheath cell tumor)

Mesenchymal hamartoma of the orbit	Mantle cell lymphoma	Vascular tumors (Masson tumor, Infantile hemangioma, lobular capillary hemangioma, lymphangiectasia, epithelioid hemangioma, hemangioblastoma, angiosarcoma)
Teratoma	Chronic lymphocytic/leukemia/small lymphocytic lymphoma	Tumors of uncertain derivation (PEComa, epithelioid sarcoma, synovial sarcoma, alveolar soft part sarcoma)
Yolk sac tumor	Diffuse large B-cell lymphoma	Osteogenic tumors of the orbital bone (Osteoma, Osteoblastoma, Osteosarcoma)
Primary orbital melanoma	Plasmacytoma	Chondrogenic tumors of the orbital bone (soft tissue chondroma, mesenchymal chondrosarcoma)
	CD30-positive lymphoproliferative disorders	Fibrous dysplasia
	T-cell lymphomas	Vascular tumors of the orbital bone Hemangioma of bone, epithelial hemangioendothelioma, angiosarcoma of bone)
	Extranodal lymphoma of mature NK or T-cell lineage	Osteoclast-rich giant cell tumors of the orbital bone (aneurysmal bone cyst, giant cell tumor of bone)
	Extramedullary myeloid sarcoma	Other tumors of the orbital bone (Ewing sarcoma)
	Histiocytic tumors (Juvenile Xanthogranuloma, Rosai Dorfman, Erdheim Chester disease, Langerhans Histiocytosis, xanthelasma, adult orbit xanthogranulomatous disease)	



FROZEN SECTION AND CYTOLOGY

SILVIA J. HERNANDEZ, MD
ROGER ALAN FECHER, MD

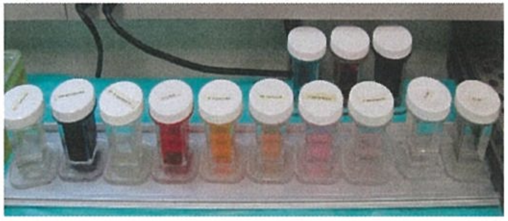
25.FROZEN SECTION AND CYTOLOGY

FROZEN SECTION AND CYTOLOGY - INTRAOPERATIVE CONSULTATION

OCT compound

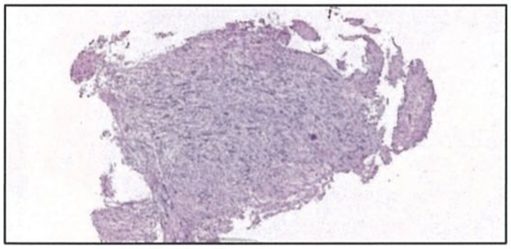
Liquid nitrogen

Cryostat

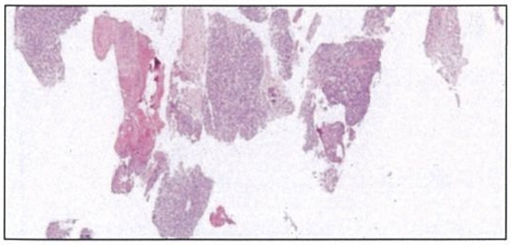


Staining solutions

Frozen section examples



Schwannoma



Chordoma

IMPORTANCE OF INTRA-OPERATIVE CONSULTATION

- Ensure that a diagnostic specimen is obtained for H&E and ancillary studies
- To obtain a preliminary diagnosis
  - Glioma vs. lymphoma – to determine the need for flow cytometry
  - Neoplastic vs. infectious – to determine the need for excision
  - High-grade glioma vs. low-grade glioma – to determine the desirable extent of surgical excision
- To evaluate the extent of a pathologic process

INTRA-OPERATIVE DIAGNOSIS IS RENDERED USING

- Frozen section(s) or cytological smear(s)

FROZEN SECTION TECHNIQUE

- Tissue is embedded in OCT (Optimal Cutting Temperature) compound
- Tissue is frozen onto a cryostat chuck utilizing a cryostat as a heat sink (or, rarely, with liquid nitrogen)
- Chuck (with tissue) is placed in the specimen head of a cryostat
- Tissue sections are cut (generally 3-10 microns thick)
- Tissue slices are picked up on glass slides and rapidly fixed
- Glass slides are stained in H&E or Diff-Quik

ADVANTAGES	DISADVANTAGES
Preservation of tissue architecture	Freezing artifact – minimized with rapid fixation
Can use frozen tissue for subsequent analysis (with or without fixation)	Cutting and processing artifacts (more common than FFPE sections)
	Drying – due to delayed fixation
	Doesn't work well with bony or calcified specimens

DIAGNOSTIC CLUES FROM GROSS INSPECTION OF TISSUE

- Bloody = Hemangioblastoma / Melanoma
- Yellow = Glioblastoma (necrosis) / Schwannoma (foamy macrophages)

DIAGNOSTIC CLUES FROM MICROSCOPIC INSPECTION

- Individual cells = Lymphomas/adenomas
- Abundant processes (cotton-like) = Gliomas
- Cellular clumps = Metastatic carcinoma

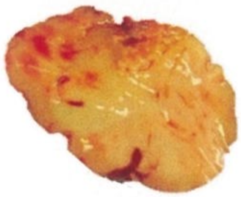


Image shows a Yellow specimen – necrosis in a glioblastoma

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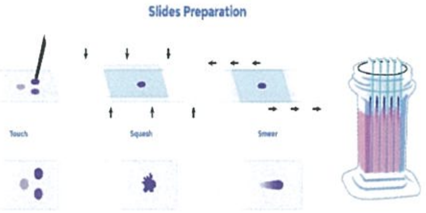
CYTOLOGY



TYPES OF CYTOLOGIC PREPARATION

TOUCH

- The tissue is touched to the glass slide (small sample)
- The slide is applied to the tissue (abundant sample)

SQUASH

- The tissue is crushed in between two slides
- The cells are separated and the matrix is flattened

SMEAR

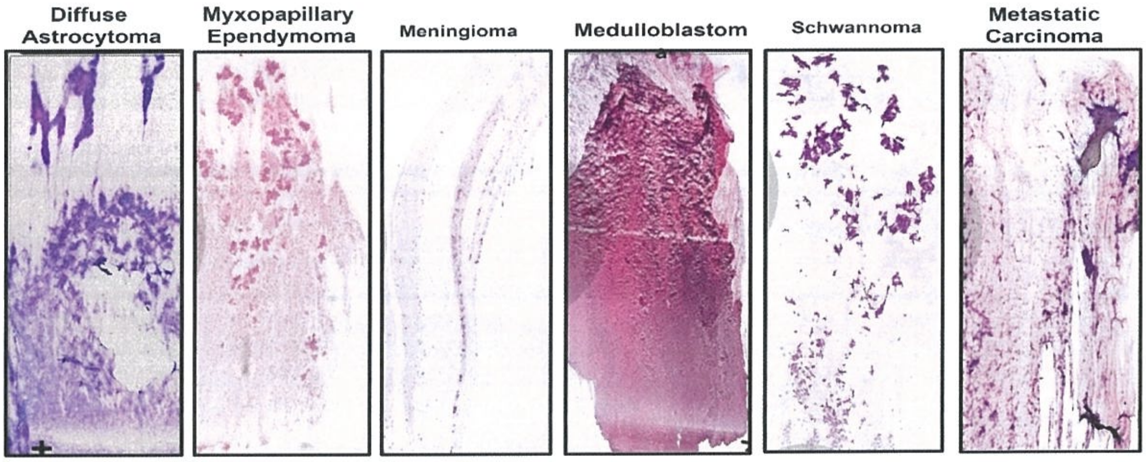
The tissue is sheared apart after it has been crushed

25.FROZEN SECTION AND CYTOLOGY

ADVANTAGES	DISADVANTAGES
Preservation of cytologic detail	Limited architecture
Quick	Only works with tissue soft enough to smear
	Cannot assess cellularity

EASY TO SMEAR	DIFFICULT TO SMEAR
Adenoma	Schwannoma
Lymphoma	Pilocytic astrocytoma
Metastasis	Ependymoma
Germinal tumor	Desmoplastic medulloblastoma
Meningioma	
Oligodendroglioma	
Embryonal tumor	

ALGORITHMIC APPROACH TO NEUROCYTOLOGY



Diffuse Astrocytoma

Myxopapillary Ependymoma

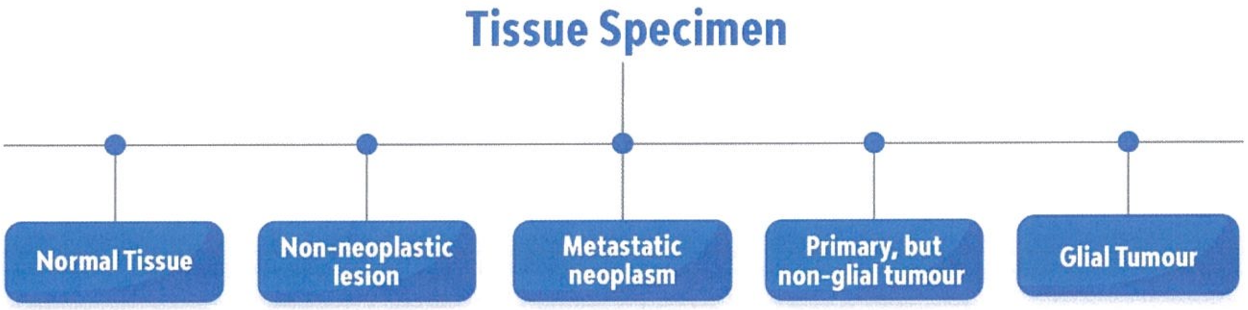
Meningioma

Medulloblastoma

Schwannoma

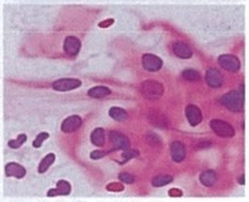
Metastatic Carcinoma

Frozen Section Decision Tree


Tissue Specimen
Normal Tissue
Non-neoplastic lesion
Metastatic neoplasm
Primary, but non-glial tumour
Glial Tumour

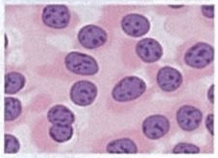
Cellular Arrangement

Cohesiveness



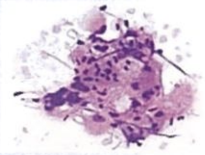
- Glioma
- Gliosarcoma
- Anaplastic meningioma
- NSGCT
- Craniopharyngioma
- Metastasis
- Nerve sheath tumor
- Choroid plexus tumor
- AT/RT
- Meningioma

Dyscohesiveness



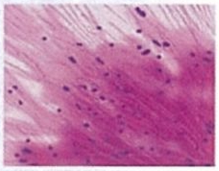
- Embryonal tumors
- PCNSL
- Pituitary adenoma

Fibrillary and cell aggregates



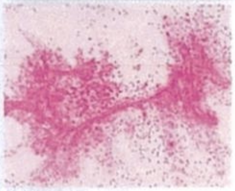
- Astrocytoma
- Glial component of
- Ganglioglioma

Fibrillary and well spaced out cells



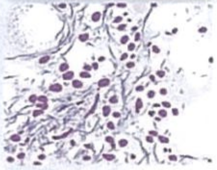
- Reactive gliosis

Papillary / Tissue fragments adhered to vessels



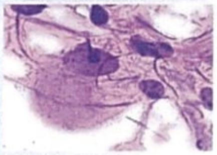
- Ependymoma
- Chorroid plexus tumors
- Papillary craniopharyngioma
- Papillary meningioma
- Rhabdoid meningioma
- PTPG
- PGNT

Floating neurons



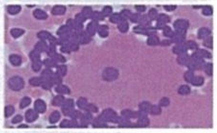
- DNET

Ample amphophilic cytoplasm



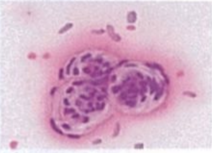
- Ganglioglioma

Small irregular rosettes with neuropil islands



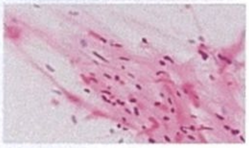
- Central neurocytoma

Meningothelial whorls



- Meningioma

Hair-like elongated with rosenthal fibres

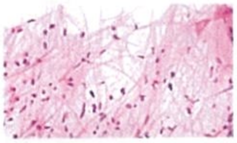


- Pilocytic astrocytoma

- DNET : Dysembrioplastic neuroepithelial tumor
- NSGCT : Non seminomatous gem cell tumor
- AT/RT : Atypical rhabdoid / teratoid tumor
- PTPG : Papillary tumor of the pineal gland
- PGNT : Papillary glioneuronal tumor
- PCNSL : Primary central nervous system lymphoma

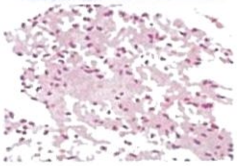
Background Features

Fibrillary



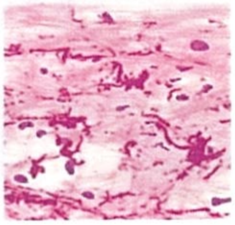
- Astrocytoma
- Ependymal tumor
- Reactive gliosis
- Oligodendroglioma
- Subependymoma
- Other Gliomas
- Glioneuronal tumors

Necrosis



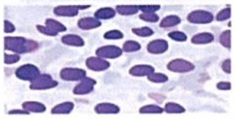
- High-grade glioma
- Post radiotherapy
- PCNSL
- Metastasis
- Germ cell tumor
- Embryonal tumors

Rosenthal fibres



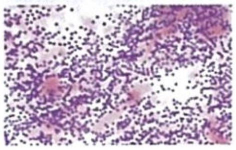
- Pilocytic astrocytoma
- Craniopharyngioma
- Hemangioblastoma

Lymphocytes



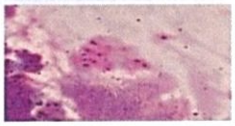
- Lymphoma
- PXA
- Germ cell tumor
- Chordoid glioma
- Ganglioglioma

Neuropil



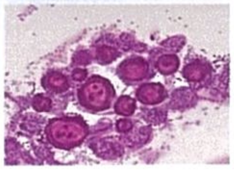
- Central neurocytoma
- Extraventricular neurocytoma
- DNT

Mixoid matrix



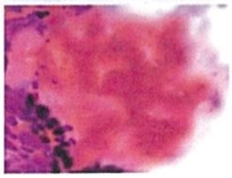
- Neurofibroma
- Chordoma
- Pilocytic astrocytoma
- Angiocentric glioma
- Myxopapillary ependymoma
- MGNT
- DNT

Psammoma bodies



- Meningioma

Keratin

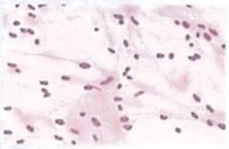


- Craniopharyngioma
- Dermoid cyst
- Epidermoid cyst
- Mature teratoma

- PXA : Pleomorphic xantho astrocytoma
- PCNSL : Primary central nervous system lymphoma
- DNT : Dysembrioplastic neuroepithelial tumor
- MGNT : Myxoid glioneuronal tumor

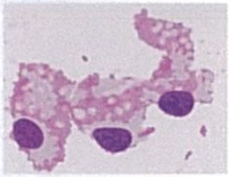
Cytoplasmic Features

Processes



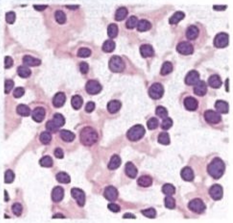
- Astrocytoma
- Ependymoma
- Meningioma
- Nerve sheath tumor

Vacuolated



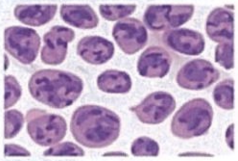
- Hemangioblastoma
- Chordoma
- Adenocarcinoma metastasis
- PXA

Dyscohesiveness



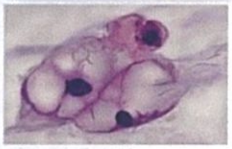
- PCNSL
- Pituitary adenoma

Scarce



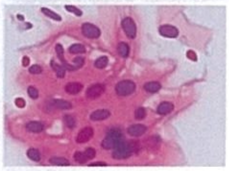
- Oligodendroglioma
- PCNSL
- Embryonal tumors

Clearing



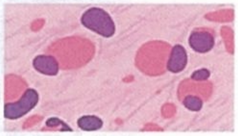
- Germ cell tumor
- Chordoma

Cohesiveness



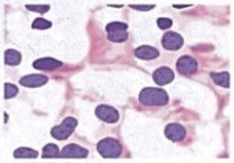
- Glioma
- Meningioma
- Germ cell tumor
- Craniopharyngioma
- Metastasis
- Nerve sheath tumor
- Choroid plexus tumor

Glassy with cell processes



- SEGA
- Gemistiocytic astrocytoma

Granular

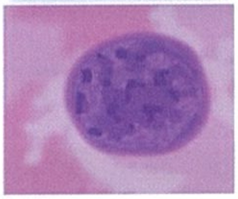


- Pituitary adenoma
- Melanoma

- SEGA : Subependymal giant cell astrocytoma
- PXA : Pleomorphic xantho astrocytoma
- PCNSL : Primary central nervous system lymphoma

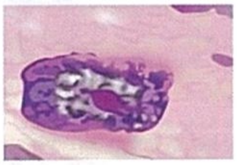
Nuclear Features

Round



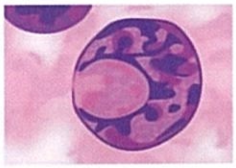
- Oligodendroglioma
- Neurocytoma
- Pituitary adenoma
- PCNSL
- PPT
- RFGNT

Prominent nucleoli



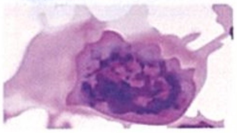
- Ependymal tumor
- Ganglioglioma
- PCNSL
- Oligodendroglioma
- Germ cell tumor
- Metastasis
- Atypical meningioma

Pseudo inclusions



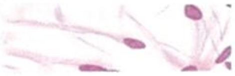
- Glioblastoma
- Meningioma
- Melanoma
- SEGA

Indentation of border



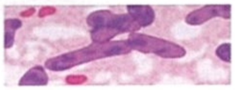
- High-grade glioma
- Chrodoma
- Embryonal tumors
- Hemangioblastoma

Oval / elongated



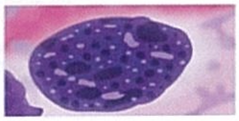
- Astrocytoma
- Ependymal tumor
- Meningioma
- Nerve sheath tumor
- Choroid plexus tumor

Hyperchromatic



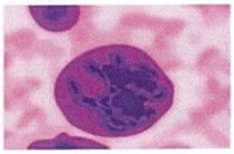
- Astrocytoma
- Pituitary adenoma
- Nerve sheath tumor
- PCNSL
- Germ cell tumor
- Embryonal tumors

Salt and pepper chromatin



- Central
- Neurocytoma
- Pituitary adenoma

Increased pleomorphism / mitosis

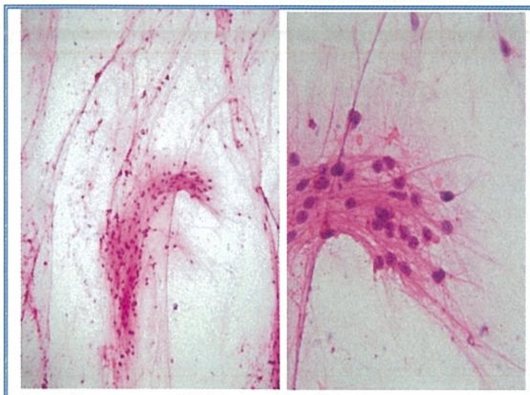


- High-grade glioma
- Metastasis
- Germ cell tumor
- AT / RT

- AT / RT : Atypical rabdoid / teratoid tumor
- PPT : pineal parenquimal tumors
- SEGA : Subependymal giant cell astrocytoma
- RFGNT : Rosette forming glioneuronal tumor

PCNSL : Primary central nervous system lymphoma

Modified from: Sharma S, Deb P. Intraoperative neurocytology of primary central nervous system neoplasia: A simplified and practical diagnostic approach. Journal Cytol October 2011;28:147-58

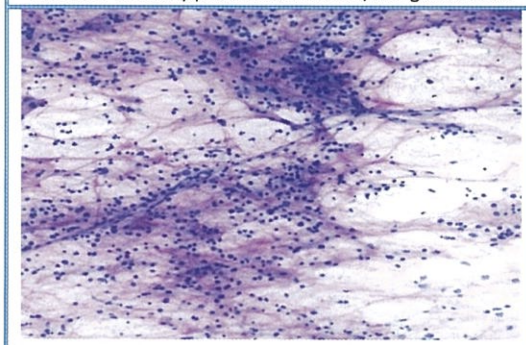


Irregular groups with increased cellularity
"Hair-like" fibrillary processes with oval/elongated nuclei

PILOCYTIC ASTROCYTOMA

MORPHOLOGY

- **Cellular arrangement: "Hair like" (piloid) processes** with oval/elongated nuclei
- **Background features:** Fibrillary "hair like" (piloid) processes +/- Rosenthal fibers and/or eosinophilic granular bodies (EGBs)
- **Cytoplasmic features:** Piloid processes
- **Nuclear features: O**val/elongated



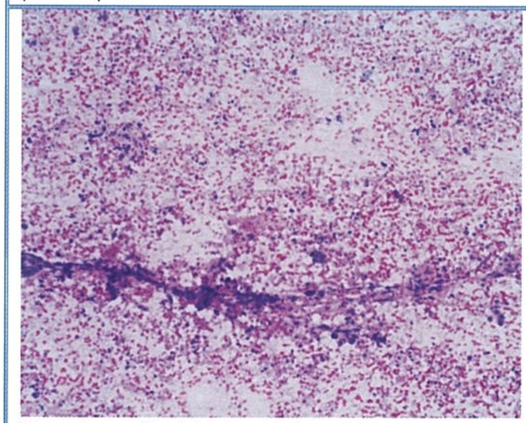
Glial background with cellular aggregates without pleomorphism

DIFFUSE ASTROCYTOMA

MORPHOLOGY

- **Cellular arrangement:** Cellular aggregates
- **Background features:** Fibrillary
- **Cytoplasmic features: Fibrillary glial processes**
- **Nuclear features:** Hyperchromatic

Path Presenter



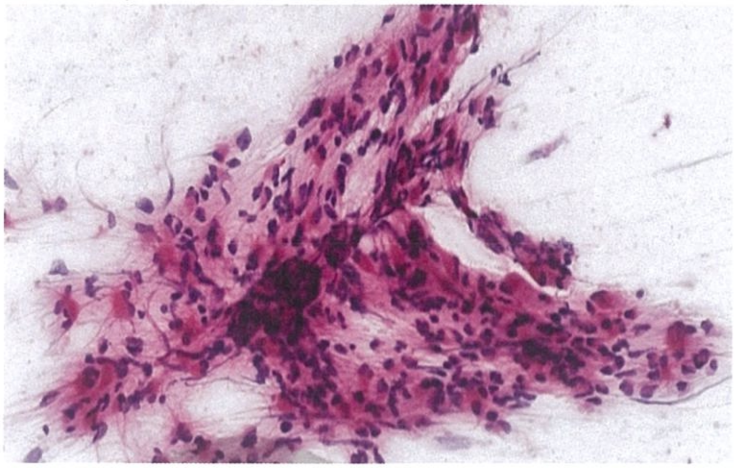
Necro-hemorrhagic background

Path Presenter

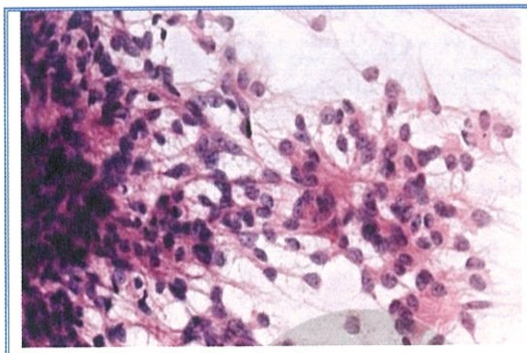
GLIOBLASTOMA

MORPHOLOGY

- **Cellular arrangement:** Fibrillary and cohesive cellular aggregates
- **Background features: Fibrillary or necrotic**
- **Cytoplasmic features: Glial processes**
- **Nuclear features:** Increased pleomorphism/mitosis or indentation of borders or pseudo inclusions



Cohesive cellularity



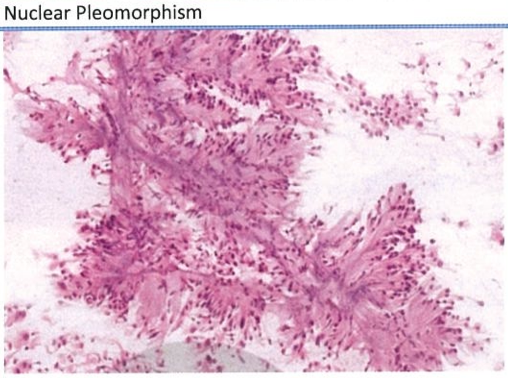
Nuclear Pleomorphism

EPENDYMOMA

MORPHOLOGY

- **Cellular arrangement: Papillary/tissue fragments** adherent to vessels or fibrillary matrix with cellular aggregates
- **Background features:** Fibrillary
- **Cytoplasmic features:** Processes, cytoplasmic hyaline globules
- **Nuclear features:** Uniform, round-oval

Path Presenter



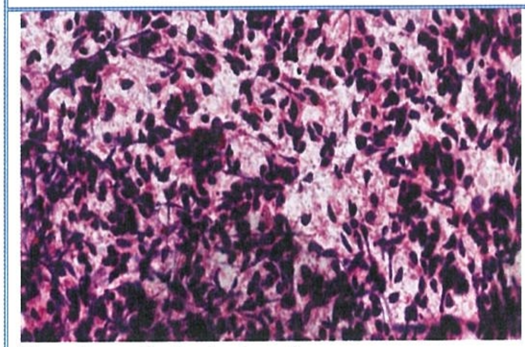
Papillary arrangement with myxoid matrix

MYXOPAPILLARY EPENDYMOMA

MORPHOLOGY

- **Cellular arrangement:** Papillary/tissue fragments adherent to vessels
- **Background features: Myxoid matrix**
- **Cytoplasmic features:** Processes, cytoplasmic hyaline globules
- **Nuclear features:** Oval-elongated

Path Presenter



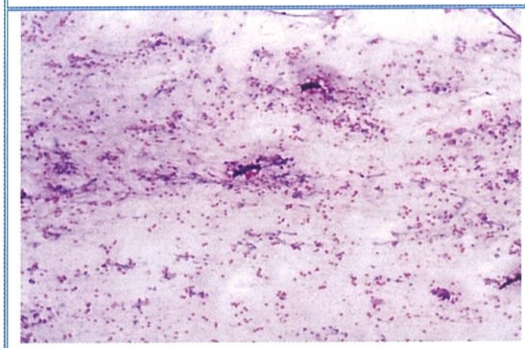
Hyperchromatic discohesive cells

MEDULLOBLASTOMA/EMBRYONAL TUMORS

MORPHOLOGY

- **Cellular arrangement:** Discohesive
- **Background features:** Necrosis
- **Cytoplasmic features: Scant cytoplasm (increased N:C ratio)**
- **Nuclear features: Hyperchromatic** (both), indentation of nuclear envelope (embryonal tumors)

Path Presenter

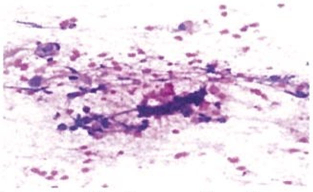


Abundant necrotic background

ATYPICAL TERATOID/RHABDOID TUMOR (AT/RT)

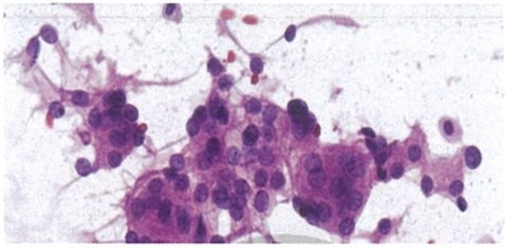
MORPHOLOGY

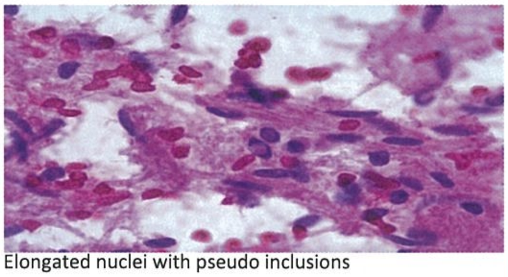
- **Cellular arrangement:** Cohesive
- **Background features:** Necrosis or Fibrillary
- **Cytoplasmic features:** Abundant eosinophilic cytoplasm with eccentric nucleus (rhabdoid)
- **Nuclear features:** Increased pleomorphism/ mitosis



Necrosis with pleomorphic cells

Cohesive cellular arrangement



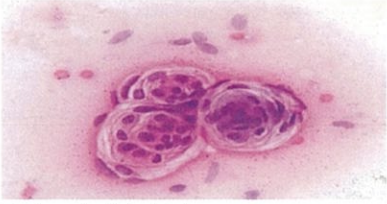


Elongated nuclei with pseudo inclusions

MENINGIOMA

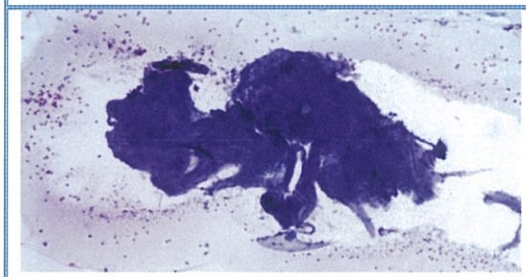
MORPHOLOGY

- **Cellular arrangement:** Cohesive cellular clusters, **meningothelial whorls**
- **Background features: Psammoma bodies**
- **Cytoplasmic features: "Blown skirt" cytoplasm**, cohesive cell clusters
- **Nuclear features:** Oval/elongated, pseudo inclusions, finely granular chromatin

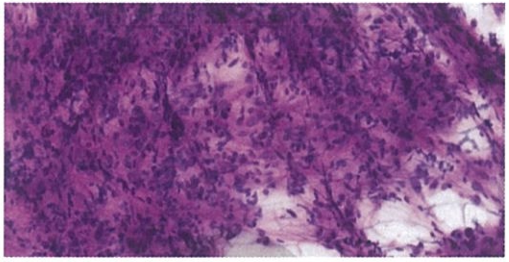


Meningothelial whorls

Path Presenter



Cohesive cellular arrangement

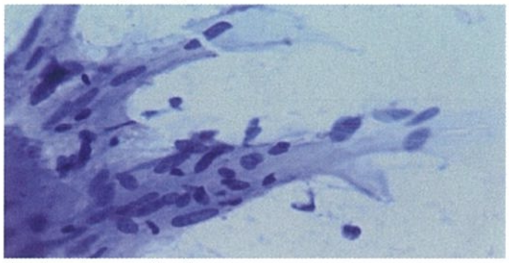


Cytoplasmic processes with cohesive cells

SCHWANNOMA/NERVE SHEATH TUMOR

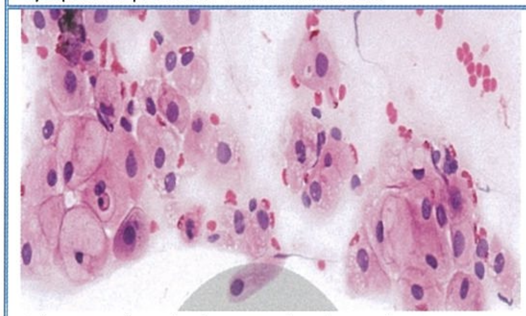
MORPHOLOGY

- **Cellular arrangement:** Cohesive cellular clusters
- **Background features:** Minimal, **smear poorly**
- **Cytoplasmic features:** Processes
- **Nuclear features:** Oval/elongated



Slender elongated cells

Path Presenter



Cohesive cells with clear vacuolated cytoplasm

CHORDOMA

MORPHOLOGY

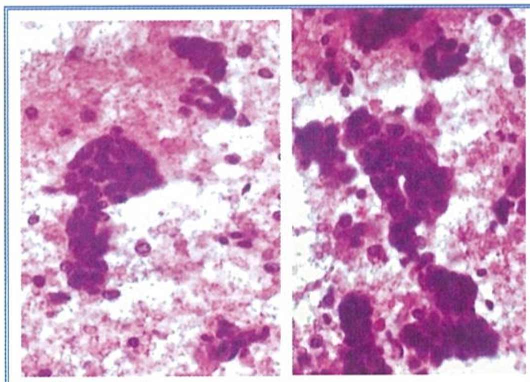
- **Cellular arrangement:** Cohesive
- **Background features: Myxoid matrix**
- **Cytoplasmic features: Bubbly/ clear vacuoles (physaliferous)**
- **Nuclear features:** Indentation of nuclear membrane

Path Presenter

CHOROID PLEXUS TUMOR

MORPHOLOGY

- **Cellular arrangement: Papillary/ tissue fragments adherent to vessels**
- **Background features:** Hemorrhagic
- **Cytoplasmic features:** Cohesive clusters
- **Nuclear features:** Oval/ elongated



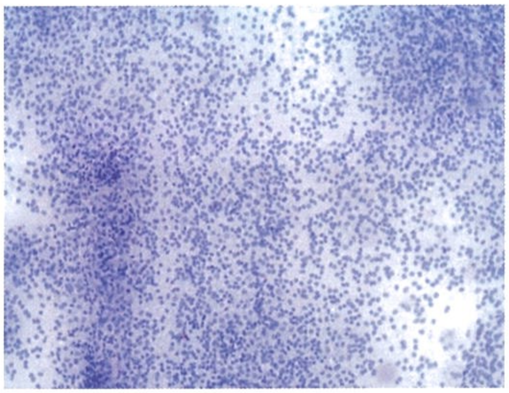
Papillary structures

Oval nuclei around papillary structures

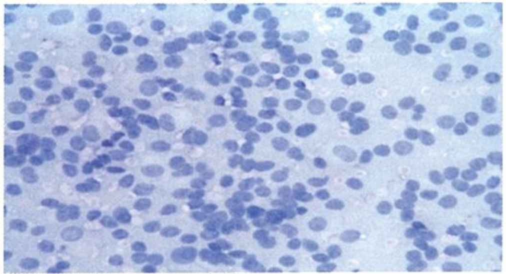
PITUITARY ADENOMA

MORPHOLOGY

- **Cellular arrangement:** Discohesive
- **Cytoplasmic features:** Discohesive
- **Nuclear features:** Salt and pepper chromatin



Discohesive

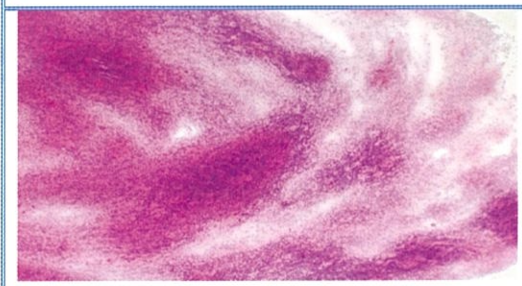


Nuclei are round with scarce cytoplasm

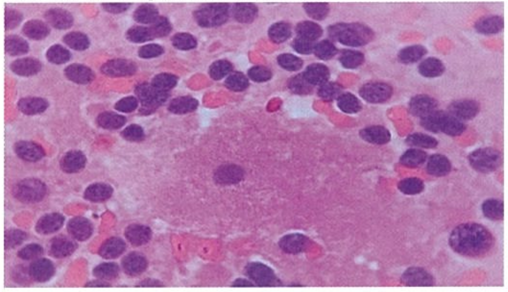
CENTRAL NEUROCYTOMA

MORPHOLOGY

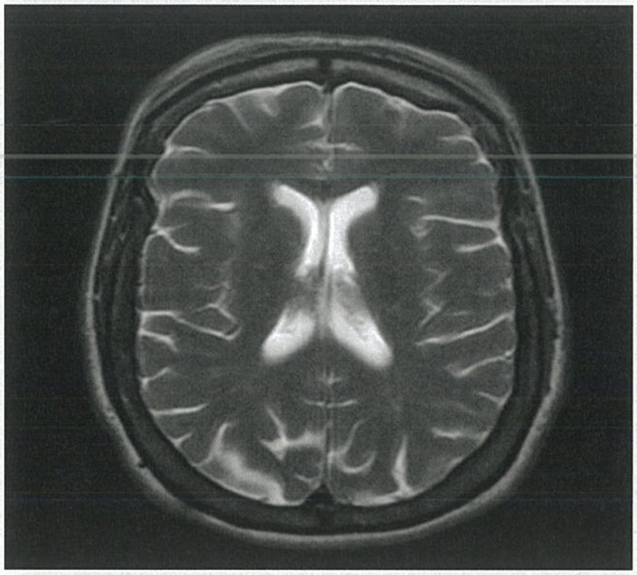
- **Cellular arrangement:** Small irregular rosettes with neuropil islands
- **Background features:** Neuropil
- **Cytoplasmic features:** Scant cytoplasm
- **Nuclear features:** Salt and pepper chromatin



Small cells arranged around neuropil



Neuropil island surrounded by small cells with salt and pepper chromatin

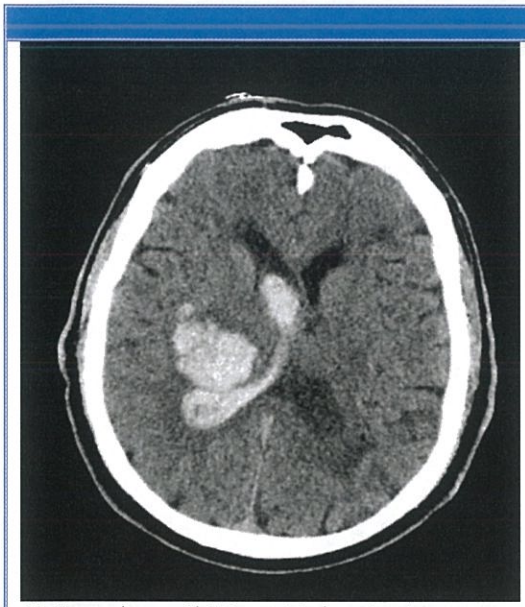


NEURORADIOLOGY

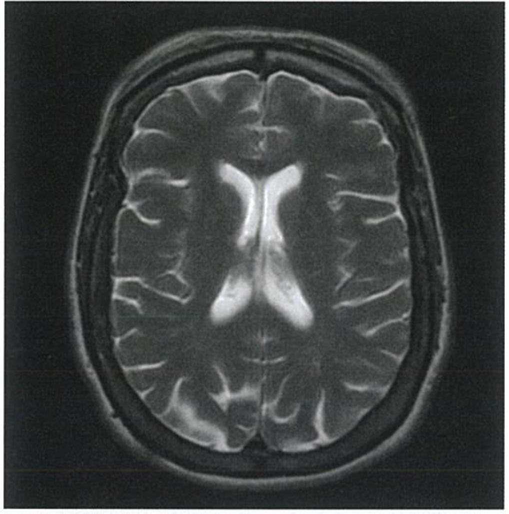
SIDDHARTHA BHANDARI, MD
ROGER ALAN FECHER, MD

26. NEURORADIOLOGY

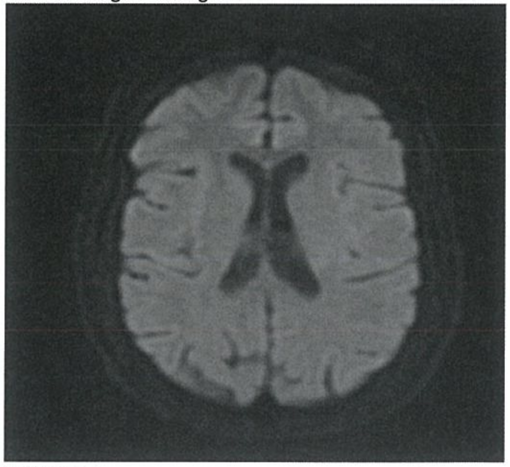
IMAGING TECHNIQUES



CT: Hemorrhage with intraventricular extension



MRI: T2-weighted image



DWI image

- Brain imaging techniques are the surrogate to gross anatomy for the neuropathologist

STANDARD TECHNIQUES

COMPUTED TOMOGRAPHY (CT)

- Analyzes X-rays in multiple axes to form slice images
- Technique of choice for bony structures
- Readily detects calcifications
- Readily available, rapid and lower cost (compared to MRI)
- Very easily and rapidly detects bleeding; first choice for suspected ICH, SAH, IVH

MAGNETIC RESONANCE IMAGING (MRI)

- It uses an external magnetic field to magnetize the protons. When these protons relax, they release energy; MRI detects the energy during relaxation to generate images
- Relaxation consists of T1 and T2 properties
- T1 weighted images are excellent for anatomy
- T2 weighted images and FLAIR are best for free water changes (seen in tumors, infection, and edema)
- FLAIR – uses fluid suppression to generate slices similar to T2-weighted images but with dark (rather than white) CSF
- Poor at imaging bony structures and calcifications

MRI technique	Water	Fat	White matter
T1-weighted	Dark	Bright	Hyperintense (white-ish) compared to gray matter
T2-weighted	Bright	Bright	Hypointense (dark-ish) compared to gray matter
FLAIR	Dark	Bright	Hypointense (dark-ish) compared to gray matter

ULTRASOUND

- The CNS is used mainly for infants whose anterior fontanelle has not closed, i.e., before 9 months of age
- Spontaneous intraventricular hemorrhage (secondary to germinal matrix hemorrhage) is diagnosed and monitored by ultrasound

ADVANCED IMAGING TECHNIQUES

DIFFUSION-WEIGHTED IMAGING (DWI)

- A form of MRI based on measuring the random Brownian movement of water molecules
- Intracellular space is very small. Therefore, intracellular water molecules cannot diffuse easily
- Extracellular space is spacious; water diffuses easily
- Intracellular water doesn't diffuse much, so it appears bright. Extracellular water diffuses easily, so it appears dark. [May remember as DWI: Detects Water Intracellular]
- Acute stroke causes ischemia. Ischemia causes cellular swelling, increasing water accumulation within the cells, reducing Brownian motion and making it easily detectable on DWI.
- Very sensitive for acute ischemia
- Uses magnets to produce images; contraindicated in patients with metallic implants, aneurysm clips, and pacemakers

26. NEURORADIOLOGY

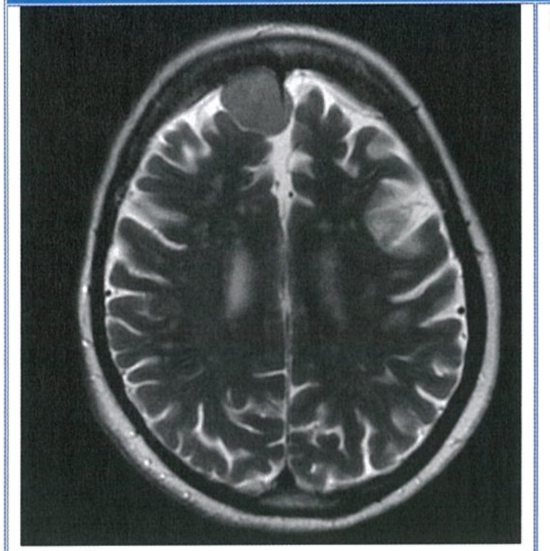
ANGIOGRAM

- Both the CT and the MRI protocols may be used to perform an angiogram to see the blood vessels
- Angiogram is used for diagnosing and treatment planning for arteriovenous malformations (AVMs), aneurysms, or narrowing due to atherosclerosis

USE OF CONTRAST

- CT scans and MRI studies may be supplemented by the use of iodine-based and gadolinium-based contrast media, respectively
- Highlights blood vessels
  - ➢ Can be used to highlight cerebral vasculature
  - ➢ Can be used to highlight tumors (neoplasms and abscesses) - secondary to increased vasculature and vascular leakage
- Contrast medium is best avoided in suspected hemorrhage
- Iodinated contrast used in CT-scans may lead to acute kidney injury
- Gadolinium based contrast used in MRI may lead to retroperitoneal fibrosis if the patient already has kidney injury

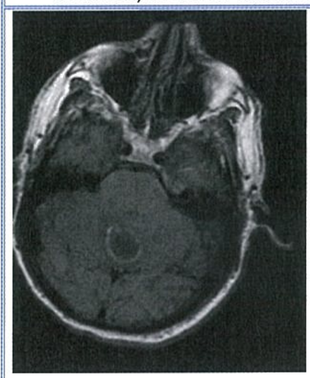
TUMORS

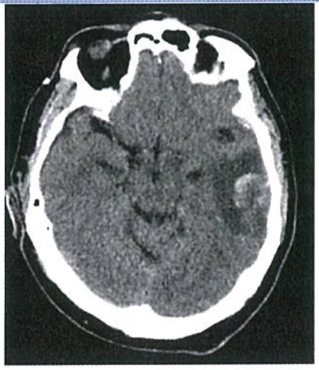

MRI (T2): MENINGIOMA

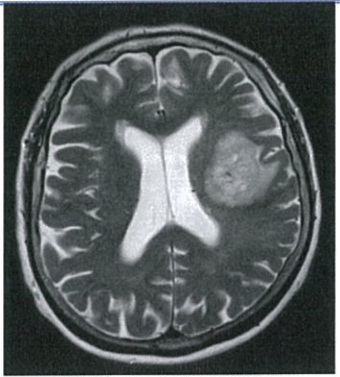
BASIC PRINCIPLES OF TUMOR IMAGING

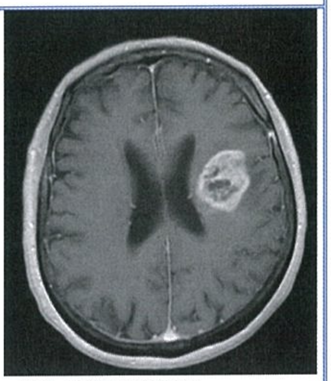
- MRI provides more detail and contrast; it is a better modality than CT for tumor identification
- CT is preferable for calcifications or bony structures
- Brightness on CT is directly proportional to the tissue density. Same is not true for MRI
- Contrast and hemorrhage both shorten T1, and so, non-contrast T1WI helps distinguish these two
- FLAIR attenuates fluids and so, it is good for evaluating tumors which are likely to be overshadowed by the fluids, e.g. the tumors located in the area around the ventricles and also the peripheral regions
- Tumor masses are crazily messed up and they interfere with the magnetic resonance. Thus, they prolong both T1 and T2. Hence, tumors are generally darker on T1WI and brighter on T2WI
- Unlike CT, where tumor calcification appears as a hyperdense area, on MRI, tumor calcification generally produces hypointensity on both T1 and T2
- Hemorrhage and fat tissue shorten the T1, and hence, appear bright on T1WI. [Remember as: Hemorrhage and Obesity (fat tissue) have a Reduced T-One (sHORTONe)]

- Contrast enhancement of any brain mass is indicative of disruption of the blood brain barrier around the mass. This can happen in high grade tumors and active inflammation
- However, this principle does not apply to certain CNS areas which do not have a blood brain barrier naturally
- On CT, brain tumors generally appear hypodense (unless calcified, in which case they show hyperdense spots) with surrounding perilesional edema. However, on MRI, they appear hypointense on T1WI & hyperintense on T2WI
- High density tumors (e.g. lymphoma, neuroblastoma) have small cells densely located in a small area leading to increased nucleus to cytoplasm (N/C) ratio, leaving less space for free water and hence, less T2 prolongation. Thus, these tumors are hypointense on T2WI

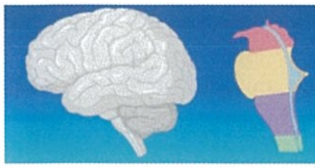

MRI: BRAIN ABSCESS


CT: HEMORRHAGIC METASTASIS


MRI (T2): GLIOBLASTOMA


MRI: GLIOBLASTOMA

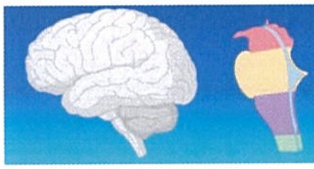
Courtesy for all images: Dr. Ranjith Chaudhary



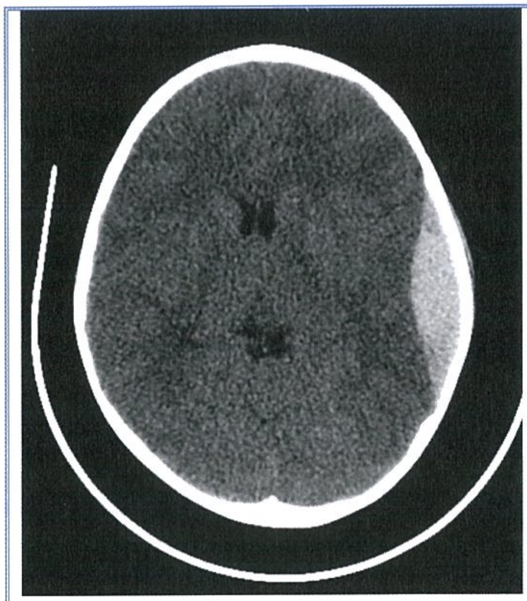
26. NEURORADIOLOGY

TUMOR IMAGING FINDINGS

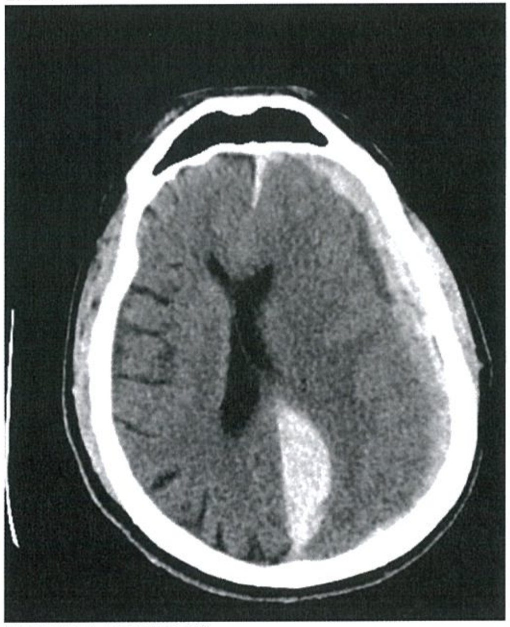
TUMOR	CT	T_1 (comp. to gray matter)	T_2 (comp. to gray matter)	Other comments
Grade I, II (low grade) astrocytoma	Hypodense	Hypointense	Hyperintense	Well circumscribed, minimal enhancement, minimal edema, no necrosis/neovascularity, no hemorrhage
High grade astrocytoma (CNS WHO grade 3, 4)	Heterogeneous	Hypo to isointense	Hyperintense	Poorly circumscribed, irregular enhancement, extensive edema, necrosis/ neovascularity, hemorrhage May see "butterfly" lesions due to bilateral involvement
Oligodendroglioma	Hypodense (with calcification spots)	Hypointense	Hyperintense	Edema not common, ring enhancement present
PCNSL	Hyperdense (as the cells are tightly packed in a lymphoma)	Hypointense	Hypointense	Edema not common, ring enhancement present
Brain metastasis	Hypodense	Hypointense		Multiple, located at gray-white junction, marked edema, marked enhancement
Medulloblastoma	Hyperdense	Hypointense	Variable (due to variable N/C ratio)	Edema
Pilocytic astrocytoma	Hypodense	Hypointense	Hyperintense	Has a cystic component, (piloCYSTIC) with an enhancing mural nodule, cystic component has protein rich fluid (and not CSF)
Hemangioblastoma	Hypodense	Hypointense	Hyperintense	Cystic component, with an enhancing mural nodule [Superficial in location because it feeds from vessels in pia]
Meningioma	Hyperdense (d/t calcification)	Hypointense	Hyperintense	Peripheral, has a dural "tail" Enhancement +++
Choroid plexus papilloma	Hyperdense (d/t calcification)	Isointense	Hyperintense	Vascular, so enhancement is +++
Craniopharyngioma	Hypodense, cystic, some calcification	Hyperintense (due to lipids)	Hyperintense	Sellar/suprasellar mass Enhancement ++
Schwannoma	Iso. to hypodense (d/t cystic degeneration)	Hypointense	Hyperintense	Enhancement +++
Pineal germinoma	Iso. to hyperdense	Hypointense	Hyperintense	Well circumscribed Enhancement +++



26. NEURORADIOLOGY



EPIDURAL HEMATOMA



SUBDURAL HEMATOMA

TRAUMA

- Trauma to the head can cause skull fracture and/or brain injury
- Brain injury can lead to primary or secondary lesions
- Primary lesions occur as a direct result of trauma, e.g. epidural hematoma, subdural hematoma, subarachnoid hemorrhage, intraventricular hemorrhage, intracerebral hematoma, diffuse axonal injury, cerebral vascular injury
- Secondary lesions occur as an effect of primary lesions and include brain edema, herniation, hydrocephalus

EPIDURAL HEMATOMA

- Occurs above dura, i.e. between dura and inner table of skull
- Epidural hematomas are Arterial in origin (E, A – both vowels), mostly from rupture of middle meningeal artery
- Epidural hematomas are Egg-shaped (or maybe almost so :P, biconvex)
- Periosteal layer of dura is firmly attached to inner table of skull at the cranial sutures which cannot be disrupted by the hematoma, and so, epidural hematoma does not cross the suture lines
- No such suture lines exist in the midline and hence, epidural hematoma crosses the midline

SUBDURAL HEMATOMA

- Occurs below dura, i.e. between dura and arachnoid
- Subdural hematomas are Venous in origin (S, V – both consonants), mostly from rupture of bridging veins
- Subdural hematomas are Sickle shaped (crescentic)
- The dura mater folds at the midline to form falx cerebri that separates right and left cerebral hemispheres, and so, SDH do not cross the midline
- The dura and the brain are not firmly attached at any point and hence, subdural hematoma may extend throughout the entirety of a hemicranium

SUBARACHNOID HEMORRHAGE

- Explained under other conditions with prominent neuroimaging findings

DIFFUSE AXONAL INJURY (DAI)

- Diffuse axonal injury occurs after acceleration/declaration injury
- As the name implies, DAI is:
  - ➢ Diffuse: Multiple injuries occur simultaneously
  - ➢ Axonal: acceleration/declaration forces cause shearing of axons, prominently around the area of axonal hillock
- Hence, the classical radiologic appearance is of multiple punctate hemorrhages, mostly at the gray-white junction
- The shearing can be non-hemorrhagic as well which can be better evaluated on an MRI
- Hence, MRI has a better sensitivity than CT scan for a DAI

Midline shift and brain herniation:

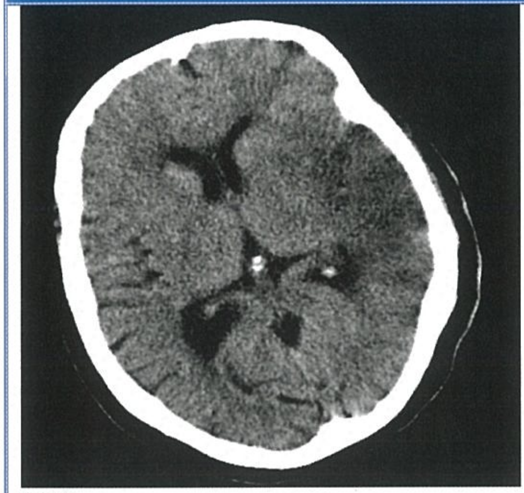
- Monro Kellie doctrine states that the cranium is a closed space, and so, an increase in the volume of one component should be accompanied by a compensatory decrease in another one.
- Acute development of hematoma or cerebral edema does not allow time for such compensation and thus, increases intracranial pressure.
- This manifests initially as midline shift and later as brain herniation
- On imaging, it is measured by measuring the perpendicular distance between the septum pellucidum (a thin cerebral tissue between right and left ventricles) and a straight line between the anterior and posterior attachments of the falx cerebri to the skull (the actual midline)
- Midline shift is an impending sign of brain herniation (shift of >3mm is significant)

26. NEURORADIOLOGY

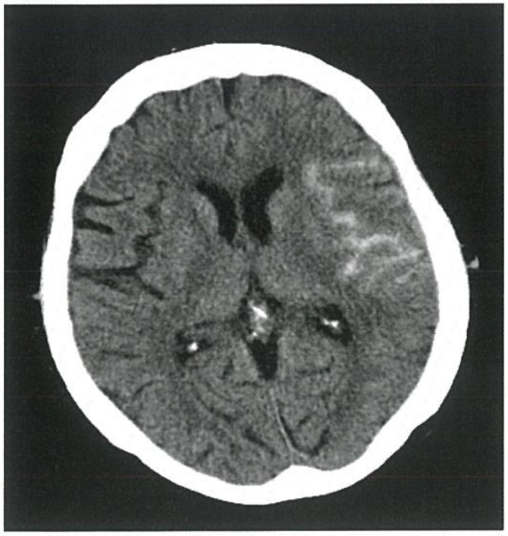
BRAIN HERNIATION

HERNIATION	DESCRIPTION	EFFECTS	RADIOLOGY
Subfalcine	Cingulate gyrus herniates under the falx cerebri	Anterior cerebral artery compressed in the midline	
Transtentorial	Vertical (downward>upward) displacement of brain stem	Shear and rupture of paramedian basilar artery branches	Increased AP axial length and decreased transverse axial length
Uncal	Uncus in medial temporal lobe herniates through the medial free edge of tentorium cerebelli	Ipsilateral CN III and contralateral crus cerebri compressed in midline	Contralateral hydrocephalus
Tonsilar	Cerebellar tonsils herniate through the foramen magnum	Brainstem compression, may lead to instant death	

ADDITIONAL CHARACTERISTIC NEUROIMAGING FINDINGS



Stroke



Subarachnoid hemorrhage

STROKE

- Rapid diagnosis directs treatment → CT is preferred over MRI
- May be hemorrhagic → avoid contrast
- May be ischemic
  - ➢ Ischemia is seen on CT around 12 hours after event
- Patient has signs and symptoms of stroke
  - ➢ Hemorrhage on CT scan → hemorrhagic stroke
  - ➢ In absence of hemorrhage, it is likely an ischemic stroke and treatment is anticoagulation or thrombolysis

SEIZURE

- Neuroimaging in seizure aims to find out a focal neurological lesion, if there is any, that is responsible for the seizure
- If a patient seizes in front of you and is in the post-ictal confusion state, a non-contrast CT is the best modality to rule out acute hemorrhage inside the brain parenchyma or in a pre-existing mass
- However, if a patient walks into the office with a history of recurrent seizures, it logical to rule out any tumor or an infection and hence, a contrast enhanced study (MRI or CT) is preferred

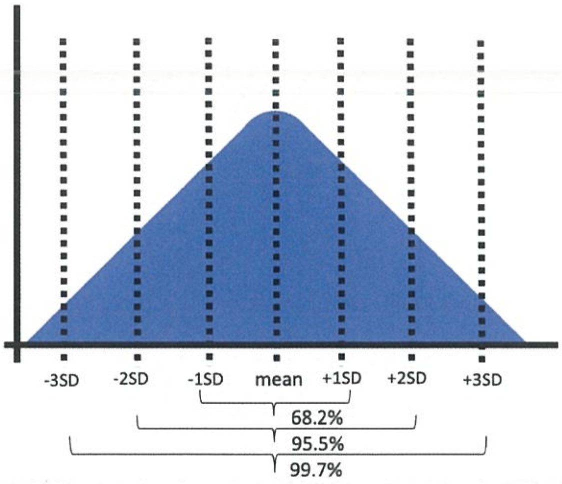
SUBARACHNOID HEMORRHAGE (+/- INTRAVENTRICULAR HEMORRHAGE)

- Subarachnoid space communicates with cerebral ventricles via foramina of Luschka (2) Laterally and foramen of Magendie (1) in the Midline and hence, on CT, SAH shows bright contents in the cerebral ventricles
- Classic clinical manifestation is a "thunderclap" headache
- Because this is hemorrhage, the imaging of choice is a non-contrast head CT
- The sulci on the surface of the brain parenchyma are filled by CSF and hence, SAH appears as sulcal brightening, with possible intraventricular extension
- Intraventricular hemorrhage leads to lysis of the blood components within the ventricles. These components settle around the ventricles and cause obstruction at the arachnoid villi or at the level of aqueduct, thus leading to hydrocephalus

26. NEURORADIOLOGY

DEMYELINATING DISORDERS: MULTIPLE SCLEROSIS AND OSMOTIC DEMYELINATION SYNDROME

- Both are demyelinating disorders occurring via different pathophysiology
- The demyelination in multiple sclerosis is autoimmune whereas that in osmotic demyelination syndrome is secondary to a rapid change in osmolality
- The lesions in both of these are hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging
- Because multiple sclerosis is an inflammatory process, the active plaques in multiple sclerosis may demonstrate contrast-enhancement
- However, as osmotic demyelination syndrome is not an inflammatory process, contrast-enhancement is not expected in the lesions in ODS
- Moreover, ODS is characterized by detachment of oligodendrocytes from the neurons, especially in the pons. This leads to diffusion restriction of water molecules causing hyperintense images on diffusion-weighted imaging
- Multiple sclerosis, on the other hand, may show increased or decreased diffusion of water molecules based on whether the inflammation is ongoing or not. Hence, the lesions may demonstrate hyperintensity or hypointensity on DWI



LAB MANAGEMENT AND INFORMATICS

PATRICIA HERNANDEZ, MD

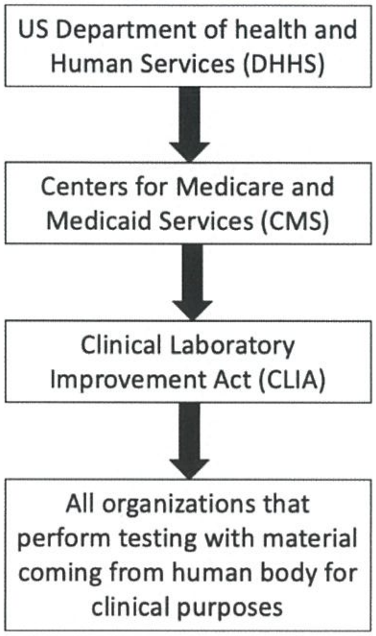
27. LAB MANAGEMENT AND INFORMATICS

LABORATORY MANAGEMENT AND INFORMATICS

- Topics in Laboratory Management focusing on Neuropathology
- Basic Concepts of Informatics

REGULATORY TOPICS

REGULATORY AGENCIES IN ANATOMIC AND CLINICAL PATHOLOGY FACILITIES



US Department of health and Human Services (DHHS)

Centers for Medicare and Medicaid Services (CMS)

Clinical Laboratory Improvement Act (CLIA)

All organizations that perform testing with material coming from human body for clinical purposes

ACCREDITATION

College of American Pathologists (CAP)

- Laboratories must be inspected every 2 years by an accrediting agency
- CAP is an accredited agency as per CMS

PROVISIONS OF ANATOMIC PATHOLOGY SERVICES

- Anatomic pathology services are provided by pathologists certified in anatomic pathology or possessing qualifications equivalent to those requested for certification. Exceptions for other qualified individuals in specific subspecialties are described below
  - A pathologist certified in anatomic pathology or possessing qualifications equivalent to those required for certification must perform services for anatomic pathology facilities
  - The services of a consulting anatomic pathologist shall be retained if necessary
  - Exception: neuromuscular pathology specimens may be interpreted by an MD or DO who is licensed to practice in the jurisdiction where the laboratory is located and has completed a training program in neuromuscular pathology approved by HHS (i.e., the American Academy of Neurology Committee for Neuromuscular Pathology Training Program)

Specimens

- Sub-optimal specimens should be documented
- The identity of every specimen is maintained at all times during the processing and examination steps
- Retention of material:
  - Gross specimens: until at least 2 weeks after the final reports are signed and results reported to the referring physician
  - Block: until at least 2 years per CLIA, CAP requires 10 years; forensic autopsy blocks should be saved indefinitely
  - Slide: until at least 10 years after the final reports are signed and results reported to the referring physician

    Test requisition and report: until at least 10 years per CAP

INFECTION CONTROL

Prevention of iatrogenic transmission of Creutzfeldt-Jakob disease (CJD)

- Disposable protective clothing should be worn (surgical cap and gown, apron, double gloves, face visor, and cut-resistant gloves)
- Manual saws are recommended to avoid the formation of aerosols
- Only individuals trained to manipulate contaminated tissues should be allowed to work in this environment
- Containers should be cleaned appropriately for the storage of formalin-fixed tissues
- Electron microscopy is not recommended for diagnostic purposes
- Body or organs coming from individuals with suspected or confirmed CJD should not be accepted by Anatomy departments for teaching or research purposes

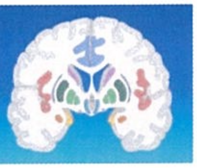
MEDICARE AND MEDICAID

- Medicare:
  - Administrated by CMS
  - Extends benefits to individuals aged 65 years or older, permanently disabled, presenting an end-stage renal disease
- Medicaid:
  - Federal program, administered by states
  - Extends benefits to individuals coming from low-income settings (specific criteria are set by states)

REIMBURSEMENT

- Medicare
  - Care is covered by parts A and B

Part A: covers hospitalization, hospice, skilled nursing facilities and home healthcare



- ➢ Part B: covers inpatient physician services
- ➢ The hospitalization costs are reimbursed according to the diagnosis-related group (DRG) which is established as a fixed amount
- ➢ CLIA certificate is required for the facility to be reimbursed by Medicare

REIMBURSEMENT SYSTEMS

- ICD (international coding of disease): describes the patient's medical condition and is used to justify billing
- HCPCS (Heath Care Procedural Coding System): utilize CPT codes that are published by the American Medical Association (AMA) for level 1 and codes developed by the AMA for level 2 (if not included in CPT)

TEST CYCLE IN NEUROPATHOLOGY

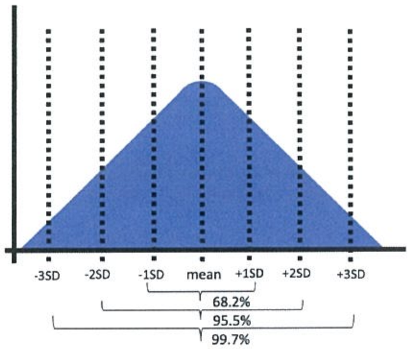
Process	Phase
Specimen collection	Pre-analytical
Requisition with adequate patient identification and history	Pre-analytical
Specimen identification	Pre-analytical
Specimen transport	Pre-analytical
Accessioning	Pre-analytical
Gross examination	Analytical
Specimen processing/ fixation	Analytical
Specimen embedding/ sectioning	Analytical
Stains	Analytical
Microscopy examination	Analytical
Report	Post-analytical
Transcription	Post-analytical

PATHOLOGY INFORMATICS

SOME DEFINITIONS

APLIS	**Anatomic pathology laboratory information system**
ASCII	American Standard Code for Information Interchange
HIS	Hospital information system
LIS	Laboratory information system
HL7	Health Level Seven International
LOINC	Logical Observation Identifies Names and Codes
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
SQL	Structured Query Language
VPN	Virtual private network

BASIC STATISTICS



DISTRIBUTION

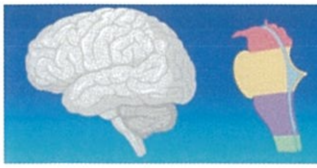
- Central tendency: mean, median and mode
- Mean = average
- Median = middle value (50th percentile)
- Mode = most frequent value
  - ➢ Gaussian: mean = median = mode

Non-Gaussian distribution

- Positively skewed: mean > median > mode
- Negatively skewed: mean < median < mode

Standard deviation and coefficient of variation

- SD =
- CV = (SD/mean) * 100



27. LAB MANAGEMENT AND INFORMATICS

ANALYTICAL ACCURACY

	DISEASE	NO DISEASE
POSITIVE TEST	True positive (TP)	False positive (FP)
NEGATIVE TEST	False negative (FN)	True negative (TN)

SENSITIVITY AND SPECIFICITY

- Sensitivity = TP / (TP + FN)
- Specificity = TN / (TN + FP)

PREDICTIVE VALUE

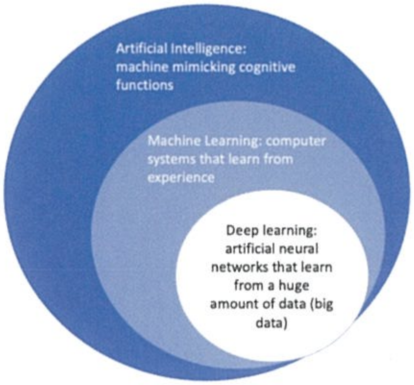
- Positive predictive value (PPV) = TP / (TP + FP)
- Negative predictive value (NPV) = TN / (TN + FN)

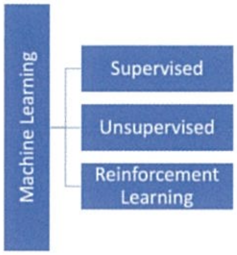
LIKELIHOOD RATIO

- LR positive = sensitivity / (1-specificity)
- LR negative = (1-sensitivity) / specificity

ARTIFICIAL INTELLIGENCE

AI vs MACHINE LEARNING vs DEEP LEARNING


Artificial Intelligence: machine mimicking cognitive functions
Machine Learning: computer systems that learn from experience
Deep learning: artificial neural networks that learn from a huge amount of data (big data)


Machine Learning
Supervised
Unsupervised
Reinforcement Learning

CATEGORIES OF MACHINE LEARNING

SUPERVISED MACHINE LEARNING

- Labeled datasets that correlate with outcomes
  - Regression: linear regression, logistic regression
  - Classification: decision tree, random forest, support vector machines

UNSUPERVISED MACHINE LEARNING

- No label datasets, which revel hidden outcomes
  - K-means clustering, anomaly detection, hierarchical clustering, principal component analysis (PCA)

REINFORCEMENT LEARNING

- Feedback-based approach in which an agent takes action based on previous action and the resulting feedback
  - Monte Carlo, Q-learning, DQN (deep Q-learning)